PCT/US98/00073

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FILE 'HOME' ENTERED AT 12:39:51 ON 06 JUL 1998

=> file medline biosis embase scisearch wpids uspatfull

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=> fas(w)ligand

L1 3121 FAS(W) LIGAND

=> s antigen presenting callas

L2 0 ANTIGEN PRESENTING CALLAS

=> s antigen presenting cells

L3 20244 ANTIGEN PRESENTING CELLS

=> s antigen

L4 899454 ANTIGEN

=> s tolerance or suppress?

3 FILES SEARCHED...
L5 1159917 TOLERANCE OR SUPPRESS?

=> s apoptosis

L6 81258 APOPTOSIS

=> s t cell or t cells or t lymphocyte or t lymphocytes

3 FILES SEARCHED...
3 FILES SEARCHED...
3 FILES SEARCHED...
5 FILES SEARCHED...
L7 586080 T CELL OR T CELLS OR T LYMPHOCYTE OR T LYMPHOCYTES

=> s adenovirus

L8 52054 ADENOVIRUS

=> s adeno-associated virus

L9 2957 ADENO-ASSOCIATED VIRUS

=> s virus or viral

3 FILES SEARCHED...
L10 1300524 VIRUS OR VIRAL

=> s alloantigen or transplantation antigen or foreign antigen

L11 17950 ALLOANTIGEN OR TRANSPLANTATION ANTIGEN OR FOREIGN ANTIGEN

=> s autoantigen or autologous antigen or homogeneic

L12 10392 AUTOANTIGEN OR AUTOLOGOUS ANTIGEN OR HOMOGENEIC

=> s autoimmune

L13 137585 AUTOIMMUNE

=> s crma

L14 511 CRMA

=> s cytotoxic t cell or cytotoxic t cell or ctl

3 FILES SEARCHED...
5 FILES SEARCHED...
L15 35119 CYTOTOXIC T CELL OR CYTOTOXIC T CELL OR CTL

=> s cd4 helper cells or cd4 cells

4 FILES SEARCHED...
L16 13699 CD4 HELPER CELLS OR CD4 CELLS

=> s gene therapy

L17 33979 GENE THERAPY

=> s inhibit?

L18 3062365 INHIBIT?

=> s transgene

L19 19608 TRANSGENE

=> s viral vector

L20 1810 VIRAL VECTOR

=> s l5 and l4 and l3 and l1

L21 17 L5 AND L4 AND L3 AND L1

=> dup rem

ENTER L# LIST OR (END):l21

PROCESSING COMPLETED FOR L21
L22 12 DUP REM L21 (5 DUPLICATES REMOVED)

=> d l22 1-12 ibib ab

L22 ANSWER 1 OF 12 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 98:247464 BIOSIS
DOCUMENT NUMBER: 01247464
TITLE: UV-induced T ***suppressor*** cells act by inducing cell death of ***antigen*** ***presenting*** ***cells*** via the Fas-***Fas*** - ***ligand*** system.
AUTHOR(S): Schwarz A; Grabbe S; Roters B; Luger T; Trinchieri G; Schwarz T
CORPORATE SOURCE: Dep. Dermatol., Univ. Muenster, Muenster, Germany
SOURCE: Annual Meeting of the International Investigative Dermatology, Cologne, Germany, May 7-10, 1998. Journal of Investigative Dermatology 110 (4). 1998. 490. ISSN: 0022-202X
DOCUMENT TYPE: Conference
LANGUAGE: English

L22 ANSWER 2 OF 12 MEDLINE
ACCESSION NUMBER: 97240749 MEDLINE
DOCUMENT NUMBER: 97240749
TITLE: Dissociation of T cell anergy from apoptosis by blockade of Fas/Apo-1 (CD95) signaling.
AUTHOR: Hargreaves R G; Borthwick N J; Montani M S; Piccolella E; Carmichael P; Lechler R I; Akbar A N; Lombardi G
CORPORATE SOURCE: Department of Immunology, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom.
CONTRACT NUMBER: CA60181 (NCI)
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 Apr 1) 158 (7) 3099-107. Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199706
ENTRY WEEK: 19970604
AB Induction of anergy and deletion due to apoptosis are two of the mechanisms involved in peripheral ***tolerance*** . To clarify the relationship between these two phenomena we have used an in vitro system of T cell Ag presentation. The recognition of Ag displayed by MHC class II-expressing T cells (T-APC) induces partial signals in Ag-specific T cell clones. This leads to a blunted intracellular calcium flux, and the T cells become unable to proliferate in response to further challenge with professional APC. These T cells are unable to produce IL-2, but retain the ability to release IL-4. In the present study, we report that for some T cell clones, the predominant outcome of Ag recognition on T cells is cell death. For susceptible T cell clones, the number of cells that die is proportional to the peptide concentration. This cell death resulted from Fas/Apo-1 (CD95)/ ***Fas*** - ***ligand*** interactions between the T cells, in that ***Fas*** ***ligand*** expression was detected following overnight culture of T cells with T-APC and neutralizing anti-CD95 Ab protected from death. Most notably, following anti-CD95-mediated protection from apoptosis, the rescued T cells remained unable to respond to rechallenge with Ag-pulsed, professional APC. These data suggest that anergy and apoptosis can be separated as consequences of partial T cell signaling.

L22 ANSWER 3 OF 12 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 97:847259 SCISEARCH
THE GENUINE ARTICLE: XY634
TITLE: Induction of specific T cell ***tolerance*** by ***Fas*** ***ligand*** expressing ***antigen*** ***presenting*** ***cells***
AUTHOR: Zhou T (Reprint); Zhang H G; Edwards C K; Bluethmann H; Mountz J D
CORPORATE SOURCE: AMGEN INC, BOULDER, CO 80301; UNIV ALABAMA, BIRMINGHAM VAMC, BIRMINGHAM, AL 35294; F HOFFMANN LA ROCHE & CO LTD, CH-4002 BASEL, SWITZERLAND
COUNTRY OF AUTHOR: USA; SWITZERLAND
SOURCE: ARTHRITIS AND RHEUMATISM, (SEP 1997) Vol. 40, No. 9, Supp. [S], pp. 517-517.
Publisher: LIPPINCOTT-RAVEN PUBL, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106.
ISSN: 0004-3591.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L22 ANSWER 4 OF 12 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 97:227250 BIOSIS
DOCUMENT NUMBER: 99518966
TITLE: Dendritic cells: From ignored cells to major players in T-cell-mediated immunity.
AUTHOR(S): Schuler G; Thurner B; Romani N
CORPORATE SOURCE: Dermatol. Universitaetsklin., Hartmannstrasse 14, D-91054 Erlangen, Germany
SOURCE: International Archives of Allergy and Immunology 112 (4). 1997. 317-322. ISSN: 1018-2438
LANGUAGE: English
AB Dendritic cells form a system of leukocytes specialized to stimulate resting T cells in vivo. Dendritic cells are crucial for the initiation of primary immune responses of both helper and cytotoxic T lymphocytes, and thus act as 'nature's adjuvant'. The manifold specializations underlying this in vivo immunostimulatory function

are becoming increasingly clear. Methods have been developed to generate large numbers of dendritic cells from hematopoletic precursors in vitro. These techniques now allow molecular studies as well as the use of antigencharged dendritic cells to vaccinate patients against tumors (e.g. B-cell lymphoma or melanoma) and infection (e.g. HIV-1). Recent data suggest that besides the classical immunostimulatory dendritic cells which belong to the myeloid lineage, there exist regulatory dendritic cells related to the lymphoid lineage. These lymphoid-derived dendritic cells which at least in part express ***Fas*** - ***ligand*** appear to be involved in the induction of central as well as peripheral ***tolerance*** , and in the future might allow a novel approach to induce ***tolerance*** in transplantation, autoimmunity, and allergy.

L22 ANSWER 5 OF 12 BIOSIS COPYRIGHT 1998 BIOSIS
ACCESSION NUMBER: 98:157778 BIOSIS
DOCUMENT NUMBER: 01157778
TITLE: Transfusion of ***Fas*** ***ligand*** expressing APCs as a therapy for autoimmune disease.
AUTHOR(S): Zhang H-G; Sun D; Curiel D T; Mountz J D; Zhou T
CORPORATE SOURCE: Univ. Ala. at Birmingham, Birmingham, AL 35294, USA
SOURCE: 61st National Scientific Meeting of the American College of Rheumatology and the 32nd National Scientific Meeting of the Association of Rheumatology Health Professionals, Washington, DC, USA, November 8-12, 1997. Arthritis & Rheumatism 40 (9 SUPPL.). 1997. S172. ISSN: 0004-3591
DOCUMENT TYPE: Conference
LANGUAGE: English

L22 ANSWER 6 OF 12 BIOSIS COPYRIGHT 1998 BIOSIS
ACCESSION NUMBER: 98:157446 BIOSIS
DOCUMENT NUMBER: 01157446
TITLE: Induction of specific T cell ***tolerance*** by ***Fas*** ***ligand*** expressing ***antigen*** ***presenting*** ***cells***
AUTHOR(S): Zhou T; Zhang H-G; Edwards C K III; Bluethmann H; Mountz J D
CORPORATE SOURCE: Univ. Ala. at Birmingham, Birmingham VAMC, Birmingham, AL 35294, USA
SOURCE: 61st National Scientific Meeting of the American College of Rheumatology and the 32nd National Scientific Meeting of the Association of Rheumatology Health Professionals, Washington, DC, USA, November 8-12, 1997. Arthritis & Rheumatism 40 (9 SUPPL.). 1997. S117. ISSN: 0004-3591
DOCUMENT TYPE: Conference
LANGUAGE: English

L22 ANSWER 7 OF 12 BIOSIS COPYRIGHT 1998 BIOSIS
ACCESSION NUMBER: 98:107315 BIOSIS
DOCUMENT NUMBER: 01107315
TITLE: Induction of allospecific T cell ***tolerance*** by treatment with ***Fas*** ***ligand*** (CD95L) positive cells.
AUTHOR(S): O'Flaherty E; Ali S; Kirby J A
CORPORATE SOURCE: Transplant Immunobiol. Unit, Dep. Surgery, Univ. Newcastle, Newcastle upon Tyne NE2 4HH, UK
SOURCE: 5th Annual Congress of the British Society for Immunology, Brighton, England, UK, December 2-5, 1997. Immunology 92 (SUPPL. 1). 1997. 84. ISSN: 0019-2805
DOCUMENT TYPE: Conference
LANGUAGE: English

L22 ANSWER 8 OF 12 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 97:379170 SCISEARCH
THE GENUINE ARTICLE: WY221
TITLE: Dendritic cells in the T-cell areas of lymphoid organs
AUTHOR: Steinman R M (Reprint); Pack M; Inaba K
CORPORATE SOURCE: ROCKEFELLER UNIV, CELLULAR PHYSIOL & IMMUNOL LAB, 1230 YORK AVE, NEW YORK, NY 10021 (Reprint); KYOTO UNIV, FAC SCI, DEPT ZOOL, KYOTO 606, JAPAN
COUNTRY OF AUTHOR: USA; JAPAN
SOURCE: IMMUNOLOGICAL REVIEWS, (APR 1997) Vol. 156, pp. 25-37. Publisher: MUNKSGAARD INT PUBL LTD, 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0105-2896.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 132
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Substantial numbers of dendritic cells (DCs) are found in the T-cell areas of peripheral lymphoid organs such as the spleen, lymph node and Peyer's patch. By electron microscopy these DCs (also called interdigitating cells) form a network through which T cells continually recirculate. The cytological features of DCs in the T-cell areas, as well as a number of markers detected with monoclonal antibodies, are similar to mature DCs that develop from other sites such as skin and bone marrow Some markers that are expressed in abundance are: MHC II and the associated invariant chain, accessory molecules such as CD40 and CD86, a multilectin receptor for ***antigen*** presentation called DEC-205, the integrin CD11c, several antigens within the endocytic system that are detected by monoclonal antibodies but are as yet uncharacterized at the molecular level, and, in the human system, molecules termed S100b, CD83 and p55. DCs in the periphery can pick up antigens and migrate to the T-cell areas to initiate immunity. However, there are new observations that DCs within the T-cell areas also express high levels of self-antigens and functional ***fas*** - ***ligand*** capable of inducing CD4(+) T-cell death. We speculate that there are at least 2 sets of DCs in the T-cell areas, a migratory myeloid pathway that brings in antigens from the periphery and induces immunity, and a more resident lymphoid pathway that presents self-antigens and maintains ***tolerance***

L22 ANSWER 9 OF 12 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 97203026 MEDLINE
DOCUMENT NUMBER: 97203026
TITLE: Interleukin 10 protects activated human T lymphocytes against growth factor withdrawal-induced cell death but only anti-fas antibody can prevent activation-induced cell death.
AUTHOR: Pawelec G; Hambrecht A; Rehbein A; Adibzadeh M
CORPORATE SOURCE: Second Department of Internal Medicine, University of Tubingen MedicalSchool, Federal Republic of Germany.. graham.pawelec@uni-tuebingen.de
SOURCE: CYTOKINE, (1996 Dec) 8 (12) 877-81. Journal code: A52. ISSN: 1043-4666.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY WEEK: 19970804
AB Interleukin 10 (IL-10) is a pleiotropic T cell-derived cytokine best known for its negative regulatory effects on T cell immunity. It inhibits responses indirectly by downregulating expression of major histocompatibility complex (MHC) molecules and co-stimulatory molecules such as CD80 on ***antigen*** ***presenting*** ***cells*** as well as directly via its effects on responding cells. On the other hand, IL-10 has been shown to protect activated T cells against apoptosis caused by withdrawal of the major growth factor, IL-2, and allow proliferation of T cells in the absence of IL-2. However, we show here that this IL-10-dependent, IL-2-independent proliferative response is short-lived, and that IL-10-responsive T cells cannot multiply in its presence. Moreover, inclusion of exogenous IL-10 in clonal cultures propagated with IL-2 results in ***suppression*** of their growth. These findings, together with the observation that IL-10 fails to protect T cells against activation-induced cell death (a fas/ ***fas*** - ***ligand*** -dependent phenomenon blocked only by certain antagonistic anti-fas reagents), suggest that the negative regulatory effects of IL-10 outweigh the upregulated proliferation observed on some T cell clones (TCC) in the absence of IL-2.

L22 ANSWER 10 OF 12 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 96:291013 SCISEARCH
THE GENUINE ARTICLE: UD905
TITLE: EFFECTS OF ***ANTIGEN*** PRESENTATION ON SUPERANTIGEN-INDUCED APOPTOSIS MEDIATED BY FAS/ ***FAS*** ***LIGAND*** INTERACTIONS IN HUMAN T-CELLS
AUTHOR: BOSHELL M; MCLEOD J; WALKER L; HALL N; PATEL Y; SANSOM D (Reprint)
CORPORATE SOURCE: BATH INST RHEUMAT DIS, TRIM BRIDGE, BATH BA1 1HD, AVON, ENGLAND (Reprint); BATH INST RHEUMAT DIS, BATH BA1 1HD, AVON, ENGLAND; UNIV BATH, SCH PHARM & PHARMACOL, BATH BA2 7AY, AVON, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: IMMUNOLOGY, (APR 1996) Vol. 87, No. 4, pp. 586-592. ISSN: 0019-2805.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 42
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Stimulation of T cells with bacterial superantigens has several distinct functional outcomes including proliferation, anergy and apoptosis. At present however, the mechanisms that dictate whether activation, anergy, or apoptosis predominate are unclear. In this study we have investigated the effects of superantigen presentation to mature superantigen-reactive human T-cell lines. Despite expressing major histocompatibility complex (MHC) class II molecules, these lines failed to proliferate in response to superantigen in the absence of ***antigen*** - ***presenting*** ***cells*** (APC) but proliferated when minimal APC were added. In the absence of APC a significant proportion of the T cells underwent apoptosis. This response was rapid, ***antigen*** dependent and largely abolished by the addition of cyclosporin A. Interestingly the response was not blocked by the addition of a number of antibodies to cell surface molecules including MHC class II and intracellular adhesion molecule-1. Using both a bioassay and messenger RNA analysis we were able to demonstrate that stimulation of these T cells with superantigen resulted in the induction of ***Fas*** - ***ligand*** expression on the T cells and furthermore, the ability of these cells to induce apoptosis was inhibited by the addition of blocking Fas antibodies as well as a Fas-Fc fusion protein. These data demonstrate that stimulation of T cells with staphylococcal enterotoxin B induces expression of ***Fas*** - ***ligand*** resulting in T-cell apoptosis; however, the final outcome of proliferation or apoptosis is determined by the presence of APC.

L22 ANSWER 11 OF 12 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 96:790628 SCISEARCH
THE GENUINE ARTICLE: VP243
TITLE: CD28-CD80/CD86 INTERACTIONS IN TESTICULAR IMMUNOREGULATION
AUTHOR: SAINIOPOLLANEN S (Reprint); SAARI T; SIMELL O; POLLANEN P
CORPORATE SOURCE: UNIV TURKU, DEPT PEDIAT, FIN-20520 TURKU, FINLAND (Reprint); TURKU UNIV, DEPT ANAT, FIN-20520 TURKU, FINLAND
COUNTRY OF AUTHOR: FINLAND
SOURCE: JOURNAL OF REPRODUCTIVE IMMUNOLOGY, (OCT 1996) Vol. 31, No. 3, pp. 145-163. ISSN: 0165-0378.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 48
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The expression of two accessory molecules on ***antigen*** - ***presenting*** ***cells*** (APC), the CD80/ B7-1 and

CD86/B7-2 antigens, was studied in the testis of normal and non-obese diabetic (NOD) mice. In addition, the effect of CD28 stimulation on ***suppression*** of lymphocytes by testicular products was investigated. The testes of 4-week old NOD mice or normal BALB/c mice and the testis of 17-21-week old BALB/c mice contained no CD80 or CD86 expressing cells. In contrast, CD80 + and CD86 + cells were present in the testis of 14-22-week old NOD mice. The CD80 + cells and most of the CD86 + cells were CD11b/CD18 negative. There were some CD11b/CD18 + cells that expressed CD86 weakly. The CD80 + and CD86 + cells were often located adjacent to the vessel walls where a leukocyte not expressing CD80 or CD86 had attached to the endothelium. Some CD80 + and CD86 + cells were present among the interstitial cells. The CD80 and CD86 antigens could not be observed in the same cells as judged from stainings in parallel sections. Stimulation of ConA-or anti-CD3 epsilon-primed peripheral blood or spleen lymphocytes with anti-CD28 was able significantly to antagonize the growth-inhibitory effect of the M(r)>5 K fraction of testis extracts, but could not abolish it with increasing concentrations of testis extract. The results suggest that T lymphocytes can not be activated locally in the testis of BALB/c and young NOD mice because of the absence of the necessary CD28 ligands, CD80 and CD86, from the APCs and because of the ***suppression*** of T lymphocytes by the testicular products. In the testis of older diabetic NOD mice lymphocyte activation may occur because the testes of these mice contain CD80 +, CD11b/CD18 -, CD86 +; CD11b/CD18 + and CD86 +; CD11b/CD18 - cells and therefore, CD28 co-stimulation. which can antagonize the ***suppressive*** effect of testis extract, may occur. The possibilities for clonal anergy in testicular immunoregulation are discussed.

L22 ANSWER 12 OF 12 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 94:678968 SCISEARCH
THE GENUINE ARTICLE: PM818
TITLE: DIFFERENTIAL ABILITY OF T(H)1 AND T(H)2 T-CELLS TO EXPRESS ***FAS*** ***LIGAND*** AND TO UNDERGO ACTIVATION-INDUCED CELL
AUTHOR: RAMSDELL F (Reprint); SEAMAN M S; MILLER R E; PICHA K S; KENNEDY M K; LYNCH D H
CORPORATE SOURCE: IMMUNEX RES & DEV CORP, DEPT IMMUNOL, SEATTLE, WA,
98101 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: INTERNATIONAL IMMUNOLOGY, (OCT 1994) Vol. 6, No. 10, pp. 1545-1553.
ISSN: 0953-8178.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 55
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Stimulation of previously activated T cells through the ***antigen*** receptor can result in the apoptotic death of the responding cell, a process referred to as activation-induced cell death (AICD). This process appears to involve Fas (CD95) and its ligand (Fas-L). The distribution of Fas and Fas-L on Various T cell subsets has not been extensively characterized. We have therefore analyzed cells committed to a T(h)1- or T(h)2-type differentiation pattern for the expression and function of Fas-L. Using both a sensitive bioassay and flow cytometry, we demonstrate that cloned T(h)1 cells express high levels of Fas-L, whereas cloned T(h)2 cells express only low levels. The expression of Fas-L by T(h)1 and T(h)2 cells correlates with the relative abilities of these two cell types to undergo AICD. Whereas AICD is readily observed in cultures of cloned T(h)1, but not T(h)2, cells, T(h)2 cells are capable of undergoing apoptosis in the presence of T(h)1 cells expressing Fas-L. The ability of T cells to undergo AICD appears to be unrelated to the presence of various cytokines. Thus, the Fas/Fas-L pathway appears to be critical for the induction of AICD and this pathway is differentially regulated in cells committed to either T(h)1 or T(h)2 differentiation.

=> s l14 and l6

L23 408 L14 AND L6

=> s l14 and l6 and l3

L24 0 L14 AND L6 AND L3

=> s l14 and l6 and l15

L25 10 L14 AND L6 AND L15

=> dupr rem

DUPR IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> dup rem

ENTER L# LIST OR (END):l25

PROCESSING COMPLETED FOR L25
L26 4 DUP REM L25 (6 DUPLICATES REMOVED)

=> d l26 1-4 ibib ab

L26 ANSWER 1 OF 4 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 1998:398780 SCISEARCH
THE GENUINE ARTICLE: ZN995
TITLE: Toxoplasma gondii-infected cells are resistant to multiple inducers of ***apoptosis***
AUTHOR: Nash P B (Reprint); Purner M B; Leon R P; Clarke P; Duke R C; Curiel T J
CORPORATE SOURCE: 1825 SHARP POINT DR, FT COLLINS, CO 80525 (Reprint);
UNIV COLORADO, HLTH SCI CTR, DEPT MED, DIV INFECT DIS, DENVER, CO 80220; UNIV COLORADO, HLTH SCI CTR, DEPT MED, DIV MED ONCOL, DENVER, CO 80220
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF IMMUNOLOGY, (15 FEB 1998) Vol. 160, No. 4, pp. 1824-1830.
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0022-1767.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 59
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Infection with certain intracellular pathogens, including viruses and bacteria, may induce host cell ***apoptosis*** . On the other hand, infection with some viruses inhibits ***apoptosis*** , Complex protozoan parasites, including Toxoplasma gondii and members of Plasmodium, Leishmania, and Microsporidia, are also obligate intracellular pathogens, get relatively little is known regarding their subversion of host cell functions. We now report that cells infected with T. gondii are resistant to multiple inducers of ***apoptosis*** , including Fas-dependent and Fas-independent ***CTL*** -mediated cytotoxicity, IL-2 deprivation, gamma irradiation, UV irradiation, and the calcium ionophore beauvericin. Inhibition of such a broad array of ***apoptosis*** inducers suggests that a mechanism common to many, or perhaps all, apoptotic pathways is involved. The inhibitory activity requires live intracellular parasite and ongoing protein synthesis. Despite T. gondii-mediated inhibition of DNA fragmentation, infected cells can still be lysed by ***CTL*** .

L26 ANSWER 2 OF 4 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 96279202 MEDLINE
DOCUMENT NUMBER: 96279202
TITLE: The CED-3/ICE-like protease Mch2 is activated during ***apoptosis*** and cleaves the death substrate lamin A.
AUTHOR: Orth K; Chinnaiyan A M; Garg M; Froelich C J; Dixit V M
CORPORATE SOURCE: Department of Pathology, University of Michigan, Ann Arbor, Michigan 48109, USA.
CONTRACT NUMBER: CA64803 (NCI)
CA68769 (NCI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Jul 12) 271 (28) 16443-6.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199610
AB Phylogenetic analysis of the CED-3/ICE family of cysteine proteases suggests the existence of a subfamily most related to the Caenorhabditis elegans death gene ced-3 and includes Yama (CPP32, apopain), LAP3 (Mch3, CMH1), and Mch2. Here, we show that Mch2 is processed from its zymogen form to a proteolytically active dimeric species during execution of the apoptotic program and by the ***cytotoxic*** ***T*** ***cell*** death protease granzyme B. Additionally, like Yama and LAP3, Mch2 functions downstream of the death inhibitors Bcl-2, Bcl-xL, and ***CrmA*** . Importantly, Mch2, but not Yama or LAP3, is capable of cleaving lamin A to its signature apoptotic fragment, indicating that Mch2 is an apoptotic laminase.

L26 ANSWER 3 OF 4 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 96:727313 SCISEARCH
THE GENUINE ARTICLE: VK361
TITLE: PROCESSING OF THE NEDD2 PRECURSOR BY ICE-LIKE PROTEASES AND GRANZYME-B
AUTHOR: HARVEY N L (Reprint); TRAPANI J A; FERNANDESALNEMRI T; LITWACK G; ALNEMRI E S; KUMAR S
CORPORATE SOURCE: INST MED & VET SCI, HANSON CTR CANC RES, ADELAIDE,
SA 5000, AUSTRALIA; AUSTIN RES INST, HEIDELBERG, VIC 3084, AUSTRALIA; JEFFERSON MED COLL, JEFFERSON CANC INST, PHILADELPHIA, PA, 19107
COUNTRY OF AUTHOR: AUSTRALIA; USA
SOURCE: GENES TO CELLS, (JUL 1996) Vol. 1, No. 7, pp. 673-685.
ISSN: 1356-9597.
DOCUMENT TYPE: Article; Journal
LANGUAGE: ENGLISH
REFERENCE COUNT: 47
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background: The Nedd2/Ich-1 protein belongs to a growing family of mammalian cysteine proteases similar to interleukin-1 beta converting enzyme (ICE). Because of their similarity to the Caenorhabditis elegans cell death protein CED-3, the ICE-like proteins are thought to play a key role in the execution of ***apoptosis*** . The active form of ICE is a tetramer consisting of two heterodimers (p20 + p10)(2) derived from the cleavage of the pro-enzyme.
Results: In the present communication we show that the p51 Nedd2 precursor (pro-Nedd2) is also cleaved into p20-like (p19) and pl0-like (p12) subunits by extracts prepared from cultured cell lines. Extracts from apoptotic NIH-3T3 cells but not normal growing NIH-3T3 cells also contained pro-Nedd2 cleaving activity. The processing of pro-Nedd2 by cell extracts was inhibited by characteristic inhibitors of ICE-like proteases. Additionally we show that pro-Nedd2 (p51) can be processed in vitro by active CPP32 and ICE, and to a lesser extent by Mch2 and Nedd2. Granzyme B, a serine protease required for cytotoxic T lymphocyte (***CTL***) mediated killing of target cells, also cleaved pro-Nedd2 to p19 + p12 subunits.
Conclusions: Our observations suggest that Nedd2 activation requires cleavage by one or more ICE-like proteases that lie upstream in the proteolytic cascade. Cleavage of pro-Nedd2 by granzyme B indicates that Nedd2 may be one of the downstream effecters in the ***CTL*** -mediated killing of target cells.

L26 ANSWER 4 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 96032689 MEDLINE
DOCUMENT NUMBER: 96032689
TITLE: ***CrmA*** , a poxvirus-encoded serpin, inhibits cytotoxic T-lymphocyte-mediated ***apoptosis*** .

AUTHOR: Tewari M; Telford W G; Miller R A; Dixit V M
CORPORATE SOURCE: Department of Pathology, University of Michigan Medical School, Ann Arbor 48109, USA.
CONTRACT NUMBER: CA61348 (NCI)
AG09801 (NIA)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Sep 29) 270 (39) 22705-8.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199601
AB Cytotoxic T-lymphocytes (CTLs), by virtue of their ability to recognize and induce apoptotic death of virus-infected cells, comprise a major antiviral defense mechanism. The induction of ***apoptosis*** by CTLs can be completely accounted for by two mechanisms: (i) a Ca(2+)-dependent component that involves the exocytotic release of serine proteases known as granzymes from ***CTL*** granules and their subsequent insertion into the target cell to induce ***apoptosis*** and (ii) a Ca(2+)-independent component that involves the activation of Fas, a receptor on the target cell membrane that triggers ***apoptosis*** . Although viruses have evolved several indirect mechanisms for evading the ***CTL*** response, direct inhibition of the apoptotic cascade has never been described. We now show for the first time that the cowpox virus protein ***CrmA*** , a protease inhibitor of the serpin family, is capable of inhibiting ***CTL*** -mediated cytolysis. The inhibitory effect is largely the result of blockade of the Ca(2+)-independent (i.e. Fas-mediated) component of ***CTL*** killing. ***CrmA*** thus represents the first example of a viral gene product capable of directly blocking ***CTL*** -mediated cell death.

=> s l17 and l1 and l3 and l5

L27 0 L17 AND L1 AND L3 AND L5

=> s l17 and l1 and l5

L28 10 L17 AND L1 AND L5

=> dup rem

ENTER L# LIST OR (END):l28

L29 7 DUP REM L28 (3 DUPLICATES REMOVED)

=> d l29 1-7 ibib ab

L29 ANSWER 1 OF 7 USPATFULL
ACCESSION NUMBER: 1998:72713 USPATFULL
TITLE: Bax omega protein and methods
INVENTOR(S): Bitler, Catherine Mastroni, Menlo Park, CA, United States
Bowersox, Stephen Scott, Menlo Park, CA, United States
Crea, Roberto, San Mateo, CA, United States
Demo, Susan Dunham, San Francisco, CA, United States
Horne, William A., San Diego, CA, United States
Zhou, Mei, Palo Alto, CA, United States
PATENT ASSIGNEE(S): Neurex Corporation, Menlo Park, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5770690	980623
APPLICATION INFO.:	US 96-616732	960315 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 95-495042, filed on 27 Jun 1995, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Ketter, James
ASSISTANT EXAMINER: Yucel, Irem
LEGAL REPRESENTATIVE: Sholtz, Charles K.; Dehlinger, Peter J.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 3023
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Bax-.omega. polynucleotides and polypeptides, and compositions effective to hybridize to Bax-.omega. polynucleotides are disclosed. Also disclosed are methods for altering apoptosis in cells, for promoting cell survival and for identifying compounds capable of affecting the binding of Bax-.omega. to other proteins involved in apoptosis.

L29 ANSWER 2 OF 7 USPATFULL
ACCESSION NUMBER: 1998:65012 USPATFULL
TITLE: DNA encoding a cytokine that induces apoptosis
INVENTOR(S): Wiley, Steven R., Seattle, WA, United States
Goodwin, Raymond G., Seattle, WA, United States
PATENT ASSIGNEE(S): Immunex Corporation, Seatlle, WA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5763223	980609
APPLICATION INFO.:	US 96-670354	960625 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 95-548368, filed on 1 Nov 1995, now abandoned which is a continuation-in-part of Ser. No. US 95-496632, filed on 29 Jun 1995, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Ulm, John
ASSISTANT EXAMINER: Mertz, Prema
LEGAL REPRESENTATIVE: Anderson, Kathryn A.
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 2248
AB A novel cytokine designated TRAIL induces apoptosis of certain target cells, including cancer cells and virally infected cells. Isolated DNA sequences encoding TRAIL are disclosed, along with expression vectors and transformed host cells useful in producing TRAIL polypeptides. Antibodies that specifically bind TRAIL are provided as well.

L29 ANSWER 3 OF 7 USPATFULL
ACCESSION NUMBER: 1998:9346 USPATFULL
TITLE: Human cell death-associated protein
INVENTOR(S): Hawkins, Phillip R., Mountain View, CA, United States
Braxton, Scott Michael, San Mateo, CA, United States
Murry, Lynn E., Portola Valley, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5712115	980127
APPLICATION INFO.:	US 96-618164	960319 (8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Chan, Christina Y.
ASSISTANT EXAMINER: Cech, Emma
LEGAL REPRESENTATIVE: Incyte Pharmaceuticals, Inc.; Billings, Lucy J.; Luther, Barbara J.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1,2
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1765
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a polynucleotide which identifies and encodes a human cell death-associated protein (cdap) which was isolated from a rheumatoid synovium library. The invention provides for genetically engineered expression vectors and host cells comprising a nucleic acid sequence encoding CDAP. The invention also provides for the therapeutic use of purified CDAP, cdap or its antisense molecules, or CDAP inhibitors in pharmaceutical compositions and for treatment of conditions or diseases associated with expression of CDAP. The invention also describes diagnostic assays which utilize diagnostic compositions comprising the polynucleotide, or fragments thereof, or antibodies which specifically bind to the polypeptide.

L29 ANSWER 4 OF 7 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998109077 EMBASE
TITLE: ***Gene*** ***therapy*** : Ovarian carcinoma as the paradigm.
AUTHOR: Gomez-Navarro J.; Siegal G.P.; Alvarez R.D.; Curiel D.T.
CORPORATE SOURCE: Dr. G.P. Siegal, Division of Anatomic Pathology, Department of Pathology, 506 Kracke Bldg, 618 S 18th St, Birmingham, AL 35233, United States Minor Outlying Islands
SOURCE: American Journal of Clinical Pathology, (1998) 109/4 (444-467).
Refs: 254
ISSN: 0002-9173 CODEN: AJCPAI
COUNTRY: United States Minor Outlying Islands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
010 Obstetrics and Gynecology
016 Cancer
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The delineation of the molecular basis of cancer in general, and of ovarian carcinoma in particular, allows for the possibility of specific intervention at the molecular level for therapeutic purposes. To this end, three main approaches have been developed: mutation compensation, molecular chemotherapy, and genetic immunopotentiation. For each of these conceptual approaches, human clinical protocols, including those specific for ovarian carcinoma, have entered phase I clinical trials to assess dose escalation, safety, and toxicity issues. However, major problems remain to be solved before these approaches can become effective and commonplace strategies for the treatment of cancer. In this regard, an examination of the applications of ***gene*** ***therapy*** for ovarian carcinoma can exemplify the rationality and the problems observed in the development of ***gene*** ***therapy*** and may illustrate prospects for their solution that are being refined, including current efforts in our laboratory. An overriding obstacle is the basic ability to deliver therapeutic genes quantitatively, and specifically, into tumor cells. As vector technology fulfills these requirements, it is anticipated that promising results already observed in preclinical studies will translate quickly into the clinical setting for amelioration of this life-threatening disease in women.

L29 ANSWER 5 OF 7 MEDLINE
ACCESSION NUMBER: 1998054326 MEDLINE
DOCUMENT NUMBER: 98054326
TITLE: Gene transfer of ***Fas*** ***ligand*** induces tumor regression in vivo.
AUTHOR: Arai H; Gordon D; Nabel E G; Nabel G J
CORPORATE SOURCE: Howard Hughes Medical Institute, University of Michigan Medical Center, 1150 West Medical Center Drive, 4520 MSRB I, Ann Arbor, MI 48109-0650, USA.
CONTRACT NUMBER: RO1 AI36606 (NIAID)
PO1 CA59327 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA (1997 Dec 9) 94 (25) 13862-7.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199803
ENTRY WEEK: 19980303
AB The Fas- ***Fas*** ***ligand*** (FasL) system plays an

important role in the induction of lymphoid apoptosis and has been implicated in the ***suppression*** of immune responses. Herein, we report that gene transfer of FasL inhibits tumor cell growth in vivo. Although such inhibition is expected in Fas+ tumor cell lines, marked regression was unexpectedly observed after FasL gene transfer into the CT26 colon carcinoma that does not express Fas. Infection by an adenoviral vector encoding FasL rapidly eliminated tumor masses in the Fas+ Renca tumor by inducing cell death, whereas the elimination of Fas- CT26 cells was mediated by inflammatory cells. Analysis of human malignancies revealed Fas, but not FasL, expression in a majority of tumors and susceptibility to FasL in most Fas+ cell lines. These findings suggest that gene transfer of FasL generates apoptotic responses and induces potent inflammatory reactions that can be used to induce the regression of malignancies.

L29 ANSWER 6 OF 7 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 1998096128 EMBASE
TITLE: Advances in the biological therapy and ***gene*** ***therapy*** of malignant disease.
AUTHOR: Hersh E.M.; Stopeck A.T.
CORPORATE SOURCE: E.M. Hersh, Arizona Cancer Center, Department of Hematology/Oncology, 1515 North Campbell Avenue, Tucson, AR 85724, United States
SOURCE: Clinical Cancer Research, (1997) 3/12 II (2623-2629). Refs: 49
ISSN: 1078-0432 CODEN: CCREF4
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Biological and ***gene*** ***therapy*** of cancer have become important components of clinical cancer research. Advances in this area are based on evidence for the presence of tumor antigens, antitumor immune responses, evasion of host control by tumors, and the recognition of host defense failure in cancer patients. These mechanisms are being corrected or exploited in the development of biological and ***gene*** ***therapy*** . Over the last decade, 9 biological therapies have received Food and Drug Administration approval, and another 12 appear promising and will likely be approved in the next few years. Our approach to ***gene*** ***therapy*** has been to allogenize tumors by the direct intratumoral injection of HLA-B7/.beta.2-microglobulin genes as plasmid DNA in a cationic lipid into patients with malignant melanoma. In four Phase I studies, we found a 36% response by the local injected tumor and a 19% systemic antitumor response. In other cancers, gene transfer, expression, and an intratumoral T-cell response were seen, but no clinical response was seen. A variety of follow-up studies with HLA-B7 and other genes are planned. Evasion of host control is now a major target of ***gene*** ***therapy*** . Strategies to overcome this include up-regulation of MHC and introduction of cell adhesion molecules into tumor cells, ***suppression*** of transforming growth factor .beta. and interleukin 10 production by tumor cells, and blockade of the ***fas*** ***ligand*** -fas interaction between tumor cells and attacking lymphocytes. With these approaches, it seems likely that ***gene*** ***therapy*** may become the fifth major modality of cancer treatment in the next decade.

L29 ANSWER 7 OF 7 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97474763 MEDLINE
DOCUMENT NUMBER: 97474763
TITLE: Amelioration of collagen-induced arthritis by CD95 (Apo-1/ ***Fas***)- ***ligand*** gene transfer.
AUTHOR: Zhang H; Yang Y; Horton J L; Samoilova E B; Judge T A; Turka L A; Wilson J M; Chen Y
CORPORATE SOURCE: Institute for Human Gene Therapy, Department of Molecular and Cellular Engineering, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1997 Oct 15) 100 (8) 1951-7.
Journal code: HS7. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104
AB Both rheumatoid arthritis and animal models of autoimmune arthritis are characterized by hyperactivation of synovial cells and hyperplasia of the synovial membrane. The activated synovial cells produce inflammatory cytokines and degradative enzymes that lead to destruction of cartilage and bones. Effective treatment of arthritis may require elimination of most or all activated synovial cells. The death factor Fas/Apo-1 and its ligand (FasL) play pivotal roles in maintaining self- ***tolerance*** and immune privilege. Fas is expressed constitutively in most tissues, and is dramatically upregulated at the site of inflammation. In both rheumatoid arthritis and animal models of autoimmune arthritis, high levels of Fas are expressed on activated synovial cells and infiltrating leukocytes in the inflamed joints. Unlike Fas, however, the levels of FasL expressed in the arthritic joints are extremely low, and most activated synovial cells survive despite high levels of Fas expression. To upregulate FasL expression in the arthritic joints, we have generated a recombinant replication-defective adenovirus carrying FasL gene; injection of the FasL virus into inflamed joints conferred high levels of FasL expression, induced apoptosis of synovial cells, and ameliorated collagen-induced arthritis in DBA/1 mice. The ***Fas*** - ***ligand*** virus also inhibited production of interferon-gamma by collagen-specific T cells. Coadministration of Fas-immunoglobulin fusion protein with the ***Fas*** - ***ligand*** virus prevented these effects, demonstrating the specificity of the ***Fas*** - ***ligand*** virus. Thus, FasL gene transfer at the site of inflammation effectively ameliorates autoimmune disease.

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L32 2 L20 AND L6 AND L1

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L32 ANSWER 1 OF 2 USPATFULL
ACCESSION NUMBER: 1998:48167 USPATFULL
TITLE: Nucleic acids encoding Fas associated proteins and screening assays using same
INVENTOR(S): Reed, John C., Carlsbad, CA, United States
Sato, Takaaki, San Diego, CA, United States
PATENT ASSIGNEE(S): La Jolla Cancer Research Foundation, La Jolla, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5747245	980505
APPLICATION INFO.:	US 94-259514	940614 (8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Zitomer, Stephanie W.
ASSISTANT EXAMINER: Rees, Dianne
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 1875
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides mammalian protein tyrosine phosphatases, human PTP-BAS type 4, human PTP-BAS type 5a and mouse PTP-BAS type 5b, each of which is a Fas-associated protein (FAP), nucleic acid molecules encoding a PTP-BAS type 4 or a PTP-BAS type 5 and antibodies specific for a PTP-BAS type 4 or for a PTP-BAS type 5. The invention also provides methods for identifying FAP's, which can associate with Fas and can modulate ***apoptosis*** . The invention also provides screening assays for identifying an agent that can effectively alter the association of a FAP with Fas and, therefore, can increase or decrease the level of ***apoptosis*** in a cell. The invention further provides methods of modulating ***apoptosis*** in a cell by introducing into the cell a nucleic acid molecule encoding a PTP-BAS or an antisense nucleotide sequence, which is complementary to a portion of a nucleic acid molecule encoding a PTP-BAS. The invention also provides a method of using a reagent that can specifically bind to a FAP to diagnose a pathology that is characterized by an increased or decreased level of ***apoptosis*** in a cell. The invention also provides methods of modulating ***apoptosis*** in a cell by contacting the cell with an agent that effectively alters the association of a FAP and Fas in a cell or alters the activity of a FAP in a cell.

L32 ANSWER 2 OF 2 USPATFULL
ACCESSION NUMBER: 97:44763 USPATFULL
TITLE: Fas associated proteins
INVENTOR(S): Reed, John C., Carlsbad, CA, United States
Sato, Takaaki, San Diego, CA, United States
PATENT ASSIGNEE(S): La Jolla Cancer Research Foundation, La Jolla, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5632994	970527
APPLICATION INFO.:	US 95-410804	950327 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 94-259514, filed on 14 Jun 1994
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Zitomer, Stephanie W.
ASSISTANT EXAMINER: Rees, Dianne
LEGAL REPRESENTATIVE: Campbell and Flores
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 19 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 1969
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides mammalian protein tyrosine phosphatases, human PTP-BAS type 4, human PTP-BAS type 5a and mouse PTP-BAS type 5b, each of which is a Fas-associated protein (FAP), nucleic acid molecules encoding a PTP-BAS type 4 or a PTP-BAS type 5 and antibodies specific for a PTP-BAS type 4 or for a PTP-BAS type 5. The invention also provides methods for identifying FAP's, which can associate with Fas and can modulate ***apoptosis*** . The invention also provides screening assays for identifying an agent that can effectively alter the association of a FAP with Fas and, therefore, can increase or decrease the level of ***apoptosis*** in a cell. The invention further provides methods of modulating ***apoptosis*** in a cell by introducing into the cell a nucleic acid molecule encoding a PTP-BAS or fragment of a PTP-BAS or an antisense nucleotide sequence, which is complementary to a portion of a nucleic acid molecule encoding a PTP-BAS. The invention also provides a method of using a reagent that can specifically bind to a FAP to diagnose a pathology that is characterized by an increased or decreased level of ***apoptosis*** in a cell. The invention also provides methods of modulating ***apoptosis*** in a cell by contacting the cell with an agent that effectively alters the association of a FAP and Fas in a cell or alters the activity of a FAP in a cell.

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L33 7 L1 AND L6 AND L11

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L34 5 DUP REM L33 (2 DUPLICATES REMOVED)

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L34 ANSWER 1 OF 5 USPATFULL
ACCESSION NUMBER: 1998:61156 USPATFULL
TITLE: Use of ***fas*** ***ligand*** to supress T-lymphocyte-mediated immune responses
INVENTOR(S): Bellgrau, Donald, Denver, CO, United States
Duke, Richard C., Denver, CO, United States
PATENT ASSIGNEE(S): University Technology Corporation, Boulder, CO, United States (U.S. corporation)

NUMBER DATE

PATENT INFORMATION: US 5759536 980602
APPLICATION INFO.: US 95-378507 950126 (8)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 94-250478, filed on 27 May 1994, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Campbell, Bruce R.
LEGAL REPRESENTATIVE: Sheridan & Ross, P.C.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
LINE COUNT: 802
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for inhibiting T-lymphocyte-mediated immune responses, including those directed against autologous and/or heterologous tissues, e.g., by a recipient mammal of a transplanted tissue, said method comprising providing the recipient mammal with ***Fas*** ***ligand*** . The ***Fas*** ***ligand*** may be provided to the recipient mammal by a variety of means, including by pump implantation or by transplantation of transgenic tissue expressing ***Fas*** ***ligand*** . Also provided is a method for diagnostic use of ***Fas*** ***ligand*** expression in improving transplantation success.

L34 ANSWER 2 OF 5 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 1998:73964 SCISEARCH
THE GENUINE ARTICLE: YR030
TITLE: Maximal proliferation of cytotoxic T lymphocytes requires reverse signaling through ***Fas*** ***ligand***
AUTHOR: Suzuki I; Fink P J (Reprint)
CORPORATE SOURCE: UNIV WASHINGTON, DEPT IMMUNOL, BOX 357650, RM H574A,
SEATTLE, WA 98195 (Reprint); UNIV WASHINGTON, DEPT IMMUNOL, SEATTLE, WA 98195
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (5 JAN 1998) Vol. 187, No. 1, pp. 123-128.
Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021.
ISSN: 0022-1007.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 30
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB ***Fas*** ***ligand*** (FasL/CD95L) is best known for its role in delivering apoptotic signals through its receptor, Fas (APO-1/CD95). In this study, we present evidence that Fast has a second role as a signaling receptor. ***Alloantigen*** -specific proliferation by multiple Fast-murine CTL lines is depressed compared to that of FasL(+) CTL lines. Fast(-) CTLs kill efficiently on a per recovered cell basis and can achieve wild-type levels of proliferation upon stimulation by optimal doses of anti-CD3, suggesting the lack of a costimulatory signal during antigen stimulation. To test this hypothesis directly, soluble FasIgG, a fusion protein of murine Fas and human IgG(1), was added to FasL(+) CTLs to demonstrate that blocking cell surface Fas-FasL interactions mimics the depression observed for Fast(-) CTLs. In addition, plate-bound FasIgG in conjunction with suboptimal anti-CD3 stimulation augments proliferative signals in FasL(+) but not Fast(-) CTLs. In contrast to these results with CD8(+) T cells, ***alloantigen*** -stimulated FasL(-) CD4(+) T cells proliferate vigorously compared to FasL(+) cells. These data demonstrate that reverse signaling through Fast is required for CTLs to achieve maximal proliferation and may provide clues to differences in the homeostatic regulation of activated CD4(+) and CD8(+) T cells during an immune response.

L34 ANSWER 3 OF 5 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 97:632005 SCISEARCH
THE GENUINE ARTICLE: XR802
TITLE: Human autoreactive and ***foreign*** ***antigen*** -specific T cells resist ***apoptosis*** induced by soluble recombinant CD95 ligand
AUTHOR: Zipp F (Reprint); Martin R; Lichtenfels R; Roth W; Dichgans J; Krammer P H; Weller M
CORPORATE SOURCE: UNIV TUBINGEN, DEPT NEUROL, HOPPE SEYLER STR 3,
D-72076 TUBINGEN, GERMANY (Reprint); NINCDS, NEUROIMMUNOL BRANCH, NIH, BETHESDA, MD 20892; GERMAN CANC RES CTR, D-6900 HEIDELBERG, GERMANY
COUNTRY OF AUTHOR: GERMANY; USA
SOURCE: JOURNAL OF IMMUNOLOGY, (1 SEP 1997) Vol. 159, No. 5, pp. 2108-2115.
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0022-1767.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 63
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Mature T cells are susceptible to activation-induced cell death in the periphery, Activation-induced cell death is thought to involve CD95/CD95 ligand interactions in vivo. Here we report that stimulated, CD45RO(+) human T cell lines specific for myelin basic protein or tetanus toroid from multiple sclerosis patients and healthy individuals resist ***apoptosis*** induced by soluble recombinant CD95 ligand in vitro, In contrast, the same CD95 ligand effectively kills Jurkat T lymphoma and human malignant glioma cells, The resistance of the T cell lines is not due to a lack of CD95 expression at the cell surface and is not overcome by coexposure to CD95 ligand and inhibitors of RNA or protein synthesis, The expression level of BCL-2 is lower in Jurkat than in Ag-specific T cells, After exposure to soluble CD95 ligand, Jurkat T cells, but not Ag-specific T cells, exhibit loss of BCL-2 and BCL-X expression whereas BAX expression is not affected, Surprisingly, Ag-specific T cells are rather sensitive to CD95 ligand expressed at the cell surface of N2A neuroblastoma cells, Accessory molecules expressed by the CD95 ligand-expressing effector cell are dispensable for ***apoptosis*** since the T cells are equally sensitive to agonistic APO-1 Ab, Further studies are required to determine whether resistance to soluble CD95 ligand-mediated ***apoptosis*** is a possible escape mechanism for T cells from peripheral deletion that may have relevance for autoimmune disorders.

L34 ANSWER 4 OF 5 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 96406971 MEDLINE
DOCUMENT NUMBER: 96406971
TITLE: The role of programmed cell death as an emerging new concept for the pathogenesis of autoimmune diseases.
AUTHOR: Mountz J D; Zhou T; Su X; Wu J; Cheng J
CORPORATE SOURCE: Department of Medicine, University of Alabama at Birmingham, USA.
SOURCE: CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY, (1996 Sep)
80 (3 Pt 2) S2-14. Ref: 103
Journal code: DEA. ISSN: 0090-1229.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199612
AB Activation-induced ***apoptosis*** is a primary mechanism for downmodulation of an immune response leading to immune homeostasis and deletion of T cells with specificities which may be harmful. These include deletion of T cells with self-specificities (autospecific) and excessively high affinity for ***foreign*** ***antigen*** which may lead to an excessively heightened immune response and septic shock. Surface molecules involved in activation-induced ***apoptosis*** involve Fas and ***Fas*** ***ligand*** (FasL), as well as the T-cell receptor (TCR) which modulates the expression and function of these molecules. Fas signaling mechanisms include the hematopoietic cell phosphatase (HCP) and sphingomyelinase, while TCR-signaling mechanisms include Nur77 and fyn kinase and unknown molecules that modulate expression of FasL. ***Apoptosis*** signals are further modulated by inhibitors or inducers of ***apoptosis*** including Bcl-2, p53, and interleukin-1 beta converting enzyme (ICE). Further understanding of the interaction of these molecules in autoimmune disease may lead to more specific therapies for immunosuppression tailored to the genetic or environmentally induced, activation-induced ***apoptosis*** defect in patients.

L34 ANSWER 5 OF 5 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96291392 EMBASE
TITLE: The role of programmed cell death as an emerging new concept for the pathogenesis of autoimmune diseases.
AUTHOR: Mountz J.D.; Zhou T.; Su X.; Wu J.; Cheng J.
CORPORATE SOURCE: LHRB 473, 701 South 19th St., Birmingham, AL 35294-0007, United States
SOURCE: Clinical Immunology and Immunopathology, (1996) 80/3 II (S2-S14).
ISSN: 0090-1229 CODEN: CLIIAT
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Activation-induced ***apoptosis*** is a primary mechanism for downmodulation of an immune response leading to immune homeostasis and deletion of T cells with specificities which may be harmful. These include deletion of T cells with self-specificities (autospecific) and excessively high affinity for ***foreign*** ***antigen*** which may lead to an excessively heightened immune response and septic shock. Surface molecules involved in activation-induced ***apoptosis*** involve Fas and ***Fas*** ***ligand*** (FasL), as well as the T-cell receptor (TCR) which modulates the expression and function of these molecules. Fas signaling mechanisms include the hematopoietic cell phosphatase (HCP) and sphingomyelinase, while TCR-signaling mechanisms include Nur77 and fyn kinase and unknown molecules that modulate expression of FasL. ***Apoptosis*** signals are further modulated by inhibitors or inducers of ***apoptosis*** including Bcl-2, p53, and interleukin-1.beta. converting enzyme (ICE). Further understanding of the interaction of these molecules in autoimmune disease may lead to more specific therapies for immunosuppression tailored to the genetic or environmentally induced, activation-induced ***apoptosis*** defect in patients.

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L36 19 DUP REM L35 (20 DUPLICATES REMOVED)

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L36 ANSWER 1 OF 19 USPATFULL
ACCESSION NUMBER: 1998:72713 USPATFULL
TITLE: Bax omega protein and methods
INVENTOR(S): Bitler, Catherine Mastroni, Menlo Park, CA,

United States
Bowersox, Stephen Scott, Menlo Park, CA, United States
Crea, Roberto, San Mateo, CA, United States
Demo, Susan Dunham, San Francisco, CA, United States
Horne, William A., San Diego, CA, United States
Zhou, Mei, Palo Alto, CA, United States
PATENT ASSIGNEE(S): Neurex Corporation, Menlo Park, CA, United States (U.S. corporation)

NUMBER DATE

PATENT INFORMATION: US 5770690 980623
APPLICATION INFO.: US 96-616732 960315 (8)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 95-495042, filed on 27 Jun 1995, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Ketter, James
ASSISTANT EXAMINER: Yucel, Irem
LEGAL REPRESENTATIVE: Sholtz, Charles K.; Dehlinger, Peter J.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 3023
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Bax-.omega. polynucleotides and polypeptides, and compositions effective to hybridize to Bax-.omega. polynucleotides are disclosed. Also disclosed are methods for altering ***apoptosis*** in cells, for promoting cell survival and for identifying compounds capable of affecting the binding of Bax-.omega. to other proteins involved in ***apoptosis*** .

L36 ANSWER 2 OF 19 USPATFULL
ACCESSION NUMBER: 1998:65012 USPATFULL
TITLE: DNA encoding a cytokine that induces ***apoptosis***
INVENTOR(S): Wiley, Steven R., Seattle, WA, United States
Goodwin, Raymond G., Seattle, WA, United States
PATENT ASSIGNEE(S): Immunex Corporation, Seattle, WA, United States (U.S. corporation)

NUMBER DATE

PATENT INFORMATION: US 5763223 980609
APPLICATION INFO.: US 96-670354 960625 (8)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 95-548368, filed on 1 Nov 1995, now abandoned which is a continuation-in-part of Ser. No. US 95-496632, filed on 29 Jun 1995, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Ulm, John
ASSISTANT EXAMINER: Mertz, Prema
LEGAL REPRESENTATIVE: Anderson, Kathryn A.
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 2248
AB A novel cytokine designated TRAIL induces ***apoptosis*** of certain target cells, including cancer cells and virally infected cells. Isolated DNA sequences encoding TRAIL are disclosed, along with expression vectors and transformed host cells useful in producing TRAIL polypeptides. Antibodies that specifically bind TRAIL are provided as well.

L36 ANSWER 3 OF 19 USPATFULL
ACCESSION NUMBER: 1998:65010 USPATFULL
TITLE: Human ***apoptosis*** -related calcium-binding protein
INVENTOR(S): Hillman, Jennifer L., San Jose, CA, United States
Goli, Surya K., Sunnyvale, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

NUMBER DATE

PATENT INFORMATION: US 5763220 980609
APPLICATION INFO.: US 96-766605 961212 (8)
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Wax, Robert A.
ASSISTANT EXAMINER: Bugaisky, Garbrile E.
LEGAL REPRESENTATIVE: Billings, Lucy J.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 2044
AB The present invention provides a human ***apoptosis*** -related calcium-binding protein (HARC) and polynucleotides which identify and encode HARC. The invention also provides genetically engineered expression vectors and host cells comprising the nucleic acid sequences encoding HARC and a method for producing HARC. The invention also provides for agonists, antibodies, or antagonists specifically binding HARC, and their use, in the prevention and treatment of diseases associated with expression of HARC. Additionally, the invention provides for the use of antisense molecules to polynucleotides encoding HARC for the treatment of diseases associated with the expression of HARC. The invention also provides diagnostic assays which utilize the polynucleotide, or fragments or the complement thereof, and antibodies specifically binding HARC.

L36 ANSWER 4 OF 19 USPATFULL
ACCESSION NUMBER: 1998:54696 USPATFULL
TITLE: Mitogen ERK kinase kinase (MEKK) assay
INVENTOR(S): Johnson, Gary L., Boulder, CO, United States
PATENT ASSIGNEE(S): National Jewish Center for Immunology & Respiratory Medicine, Denver, CO, United States (U.S. corporation)

NUMBER DATE

PATENT INFORMATION: US 5753446 980519
APPLICATION INFO.: US 95-472934 950606 (8)
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 94-323460, filed on 14 Oct 1994 And Ser. No. US 95-440421, filed on 12 May 1995 which is a continuation-in-part of Ser. No. US 95-354516, filed on 21 Feb 1995, now abandoned which is a division of Ser. No. US 93-49254, filed on 15 Apr 1993, now patented, Pat. No. US 5405941, issued on 11 Apr 1995 , said Ser. No. US -323460 which is a continuation-in-part of Ser. No. US -49254
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Walsh, Sephen
ASSISTANT EXAMINER: Sorensen, Kenneth A.
LEGAL REPRESENTATIVE: Lahive & Cockfield, LLP; DeConti, Jr., Giulio A.; Kara, Catherine J.
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 2314
AB The present invention relates to isolated MEKK proteins, nucleic acid molecules having sequences that encode such proteins, and antibodies raised against such proteins. The present invention also includes methods useful for identifying compounds capable of specifically regulating signal transduction in cells expressing MEKK protein.

L36 ANSWER 5 OF 19 USPATFULL
ACCESSION NUMBER: 1998:9346 USPATFULL
TITLE: Human cell death-associated protein
INVENTOR(S): Hawkins, Phillip R., Mountain View, CA, United States
Braxton, Scott Michael, San Mateo, CA, United States
Murry, Lynn E., Portola Valley, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

NUMBER DATE

PATENT INFORMATION: US 5712115 980127
APPLICATION INFO.: US 96-618164 960319 (8)
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Chan, Christina Y.
ASSISTANT EXAMINER: Cech, Emma
LEGAL REPRESENTATIVE: Incyte Pharmaceuticals, Inc.; Billings, Lucy J.; Luther, Barbara J.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1,2
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1765
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a polynucleotide which identifies and encodes a human cell death-associated protein (cdap) which was isolated from a rheumatoid synovium library. The invention provides for genetically engineered expression vectors and host cells comprising a nucleic acid sequence encoding CDAP. The invention also provides for the therapeutic use of purified CDAP, cdap or its antisense molecules, or CDAP inhibitors in pharmaceutical compositions and for treatment of conditions or diseases associated with expression of CDAP. The invention also describes diagnostic assays which utilize diagnostic compositions comprising the polynucleotide, or fragments thereof, or antibodies which specifically bind to the polypeptide.

L36 ANSWER 6 OF 19 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1998157983 MEDLINE
DOCUMENT NUMBER: 98157983
TITLE: Interaction of the ***adenovirus*** 14.7-kDa protein with FLICE inhibits ***Fas*** ***ligand*** -induced ***apoptosis*** .
AUTHOR: Chen P; Tian J; Kovesdi I; Bruder J T
CORPORATE SOURCE: GenVec, Inc., Rockville, Maryland 20852, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Mar 6) 273 (10) 5815-20.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199806
ENTRY WEEK: 19980602
AB ***Adenovirus*** type 5 encodes a 14.7-kDa protein that protects infected cells from tumor necrosis factor-induced cytolysis by an unknown mechanism. In this report, we demonstrate that infection of cells with an ***adenovirus*** vector expressing ***Fas*** ***ligand*** induced rapid ***apoptosis*** that was blocked by coinfection with a virus expressing 14. 7K. Moreover, AdFasL/G infection resulted in the rapid activation of DEVD-specific caspases, and caspase activation was blocked by coinfection with Ad14.7/G. Cell death induced by the overexpression of ***Fas*** ***ligand*** , Fas-associated death domain-containing protein (FADD)/MORT1, or FADD-like interleukin-1beta-converting enzyme (FLICE)/caspase-8 in a virus-free system was efficiently blocked by 14.7K expression. Moreover, we demonstrate that 14.7K interacts with FLICE. These results support the idea that FLICE is a cellular target for the 14.7-kDa protein.

L36 ANSWER 7 OF 19 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 1998:152973 SCISEARCH
THE GENUINE ARTICLE: YX013
TITLE: Application of a ***Fas*** ***ligand*** encoding a recombinant ***adenovirus*** vector for prolongation of transgene expression
AUTHOR: Zhang H G; Bilbao G; Zhou T; Contreras J L; GomezNavarro J; Feng M Z; Saito I; Mountz J D; Curiel D T (Reprint)
CORPORATE SOURCE: UNIV ALABAMA, GENE THERAPY PROGRAM, DEPT RHEUMATOL, 1824 6TH AVE S, WTI 620, BIRMINGHAM, AL 35294 (Reprint); UNIV ALABAMA, GENE THERAPY PROGRAM, DEPT RHEUMATOL, BIRMINGHAM, AL 35294; UNIV ALABAMA, GENE THERAPY PROGRAM, DEPT SURG, BIRMINGHAM, AL 35294; UNIV TOKYO, INST MED SCI, GENET MOL LAB, TOKYO, JAPAN

COUNTRY OF AUTHOR: USA; JAPAN
SOURCE: JOURNAL OF VIROLOGY, (MAR 1998) Vol. 72, No. 3, pp. 2483-2490.
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0022-538X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 66
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB An ***adenovirus*** vector encoding murine ***Fas*** ***ligand*** (mFasL) under an inducible control was derived. In vivo ectopic expression of mFasL in murine livers induced an inflammatory cellular infiltration. Furthermore, ectopic expression of mFasL by myocytes did not allow prolonged vector-mediated transgene expression. Thus, ectopic expression of functional mFasL in vector-transduced cells does not appear to confer, by itself, an immunoprivileged site sufficient to mitigate ***adenovirus*** vector immunogenicity.

L36 ANSWER 8 OF 19 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1998115900 MEDLINE
DOCUMENT NUMBER: 98115900
TITLE: ***Fas*** ***ligand*** gene transfer to the vessel wall inhibits neointima formation and overrides the ***adenovirus*** -mediated T cell response.
AUTHOR: Sata M; Perlman H; Muruve D A; Silver M; Ikebe M; Libermann T A; Oettgen P; Walsh K
CORPORATE SOURCE: Division of Cardiovascular Research, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, MA 02135, USA.
CONTRACT NUMBER: AG-15052 (NIA)
HL-50692 (NHLBI)
AR-40197 (NIAMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF
THE UNITED STATES OF AMERICA, (1998 Feb 3) 95 (3) 1213-7.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199805
ENTRY WEEK: 19980502
AB Proliferation of vascular smooth muscle cells (VSMCs) in response to injury plays a key role in the pathogenesis of vascular disorders. ***Fas*** ***ligand*** (FasL) induces ***apoptosis*** in Fas-bearing cells, and its expression on activated T cells contributes to the regulation of the immune response and physiological cell turnover. Here, we show that a replication-defective ***adenovirus*** encoding FasL (Ad-FasL) induced ***apoptosis*** in Fas-bearing VSMCs. When introduced locally to balloon-injured rat carotid arteries, a well characterized model of a VSMC-derived lesion, Ad-FasL functioned as a potent inhibitor of neointima formation. In rats immunized with an empty adenoviral vector, robust T cell infiltration of the vessel wall was detected after local delivery of a beta-galactosidase-expressing virus (Ad-betagal), whereas T cell infiltrates were not detected after local delivery of Ad-FasL. Prior immunization prevented beta-galactosidase expression from Ad-betagal, whereas the expression of the FasL transgene was unaffected. When Ad-betagal and Ad-FasL were delivered together to preimmunized animals, T cell infiltration was reduced and beta-galactosidase expression was restored. These data demonstrate that ***Fas*** ***ligand*** gene transfer can effectively inhibit injury-induced vessel lesion formation and can allow ***adenovirus*** -harboring cells to evade immune destruction.

L36 ANSWER 9 OF 19 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 3
ACCESSION NUMBER: 98:256744 BIOSIS
DOCUMENT NUMBER: 01256744
TITLE: FasL induces Fas-Apo1-mediated ***apoptosis*** in human embryonic kidney 293 cells routinely used to generate E1-deleted adenoviral vectors.
AUTHOR(S): Larregina A T; Morelli A E; Dewey R A; Castro M G; Fontana A; Lowenstein P R
CORPORATE SOURCE: Molecular Med. Unit, Room 1.302 Stopford Build., Dep. Med., Univ. Manchester, Oxford Road, Manchester M13 9PT, UK
SOURCE: Gene Therapy 5 (4). 1998. 563-568. ISSN: 0969-7128
LANGUAGE: English
AB Human embryonic kidney 293 cells contain the E1 region of ***adenovirus*** type 5, and thus sustain, through transcomplementation, the production of recombinant E1-deleted ***adenovirus*** vectors. During attempts to produce recombinant ***adenovirus*** expressing the ***apoptosis*** -inducing molecule ***Fas*** ***ligand*** (FasL) under the control of a very strong truncated major immediate-early human cytomegalovirus (MIEhCMV) promoter, we discovered that 293 cells were not surviving the initial cotransfection with a shuttle plasmid encoding the mouse FasL; and pJM17, a plasmid containing the genome of ***adenovirus*** type 5 with deletions in the E1-E3 regions, in an unpackagable form. Investigation of the reason for massive cell death after contransfection led us to determine that 293 cells express the FasL receptor, Fas-Apo1 (CD95), and respond with ***apoptosis*** to the cross-linking of Fas-Apo1 with either IgM monoclonal antibodies or FasL. Therefore, we decided to generate adenoviral vectors expressing FasL under the control of tissue-specific and/or -inducible promoter elements. Our findings can explain difficulties several groups have had in generating recombinant adenoviral vectors expressing FasL using 293 cells, as well as the lower titres reported.

L36 ANSWER 10 OF 19 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998117211 MEDLINE
DOCUMENT NUMBER: 98117211
TITLE: ***Fas*** ***ligand*** gene transfer to renal allografts in rats: effects on allograft survival.
AUTHOR: Swenson K M; Ke B; Wang T; Markowitz J S; Maggard M A; Spear G S; Imagawa D K; Goss J A; Busuttil R W; Seu P
CORPORATE SOURCE: Dumont-UCLA Transplant Center, Department of Surgery, UCLA School of Medicine, Cedars-Sinai Medical Center, Los Angeles, California 90095, USA.
SOURCE: TRANSPLANTATION, (1998 Jan 27) 65 (2) 155-60.
Journal code: WEJ. ISSN: 0041-1337.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199804
ENTRY WEEK: 19980402
AB BACKGROUND: ***Fas*** ***ligand*** (FasL) induces ***apoptosis*** of cells bearing its receptor Fas, and has been shown to be important in T-cell development and regulation and in immune privilege. We hypothesized that FasL expression by renal allografts might provide protection from rejection. METHODS: The murine FasL cDNA was cloned into a replication-defective ***adenovirus*** (AdV-FasL). Protein expression was confirmed by immunostaining of AdV-FasL-transduced HeLa cells. Allogeneic kidney transplants were performed between WF (RT1u) donors and Lewis (RT1) recipients. Donor kidneys were perfused in situ with saline alone (control), or 9 x 10(9) plaque-forming units of AdV-FasL. One native kidney was removed at the time of transplant and the other at 6 or 7 days. Uremic death was the endpoint, and deaths within 7 days of transplant were excluded. Transduced allografts were stained for FasL expression using a monoclonal antibody and tested for FasL mRNA production by reverse transcriptase-polymerase chain reaction and Northern blotting. RESULTS: Immunostaining of AdV-FasL-transduced allografts demonstrated efficient gene transfer lasting approximately 2 weeks, and FasL mRNA production in the AdV-FasL-transduced allografts was confirmed by Northern blotting and reverse transcriptase-polymerase chain reaction. Mean survival of animals with AdV-FasL-transduced renal allografts was 27.8 days vs. 11.6 days in control animals ($P < 0.05$). CONCLUSIONS: (1) Adenoviral vectors can successfully transduce rat kidneys with the FasL cDNA. (2) FasL gene transfer prolongs rat renal allograft survival.

L36 ANSWER 11 OF 19 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998037692 MEDLINE
DOCUMENT NUMBER: 98037692
TITLE: A major human immunodeficiency virus type 1-initiated killing pathway distinct from ***apoptosis*** .
AUTHOR: Kolesnitchenko V; King L; Riva A; Tani Y; Korsmeyer S J; Cohen D I
CORPORATE SOURCE: Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892-4255, USA.
SOURCE: JOURNAL OF VIROLOGY, (1997 Dec) 71 (12) 9753-63.
Journal code: KCV. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199803
ENTRY WEEK: 19980301
AB We have investigated the relative contribution of ***apoptosis*** or programmed cell death (PCD) to cell killing during acute infection with T-cell-tropic, cytopathic human immunodeficiency virus type 1 (HIV-1), by employing diverse strategies to inhibit PCD or to detect its common end-stage sequelae. When Bcl-2-transfected cell lines were infected with HIV-1, their viability was only slightly higher than that of control infections. Although the ***adenovirus*** E1B 19-kDa protein has been reported to be a stronger competitor of ***apoptosis*** than Bcl-2, it did not inhibit HIV-mediated cell death better than Bcl-2 protein. Competition for ***Fas*** ***ligand*** or inactivation of the Fas pathway secondary to intracellular mutation (MOLT-4 T cells) also had modest effects on overall cell death during acute HIV infection. In contrast to these observations with HIV infection or with HIV envelope-initiated cell death, Tat-expressing cell lines were much more susceptible (200% enhancement) to Fas-induced ***apoptosis*** than controls and Bcl-2 overexpression strongly (75%) inhibited this apoptotic T-cell death. PCD associated with FasR ligation resulted in the cleavage of common interleukin-1beta-converting enzyme (ICE)-protease targets,. poly(ADP-ribose) polymerase (PARP) and pro-ICE, whereas cleaved products were not readily detected during HIV infection of peripheral blood mononuclear cells or T-cell lines even during periods of extensive cell death. These results indicate that one important form of HIV-mediated cell killing proceeds by a pathway that lacks the characteristics of T-cell ***apoptosis*** . Our observations support the conclusion that at least two HIV genes (env and tat) can kill T cells by distinct pathways and that an envelope-initiated process of T-cell death can be discriminated from ***apoptosis*** by many of the properties most closely associated with apoptotic cell death.

L36 ANSWER 12 OF 19 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97474763 MEDLINE
DOCUMENT NUMBER: 97474763
TITLE: Amelioration of collagen-induced arthritis by CD95 (Apo-1/ ***Fas***)- ***ligand*** gene transfer.
AUTHOR: Zhang H; Yang Y; Horton J L; Samoilova E B; Judge T A; Turka L A; Wilson J M; Chen Y
CORPORATE SOURCE: Institute for Human Gene Therapy, Department of Molecular and Cellular Engineering, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1997 Oct 15) 100 (8) 1951-7.
Journal code: HS7. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104
AB Both rheumatoid arthritis and animal models of autoimmune arthritis

are characterized by hyperactivation of synovial cells and hyperplasia of the synovial membrane. The activated synovial cells produce inflammatory cytokines and degradative enzymes that lead to destruction of cartilage and bones. Effective treatment of arthritis may require elimination of most or all activated synovial cells. The death factor Fas/Apo-1 and its ligand (FasL) play pivotal roles in maintaining self-tolerance and immune privilege. Fas is expressed constitutively in most tissues, and is dramatically upregulated at the site of inflammation. In both rheumatoid arthritis and animal models of autoimmune arthritis, high levels of Fas are expressed on activated synovial cells and infiltrating leukocytes in the inflamed joints. Unlike Fas, however, the levels of FasL expressed in the arthritic joints are extremely low, and most activated synovial cells survive despite high levels of Fas expression. To upregulate FasL expression in the arthritic joints, we have generated a recombinant replication-defective ***adenovirus*** carrying FasL gene; injection of the FasL virus into inflamed joints conferred high levels of FasL expression, induced ***apoptosis*** of synovial cells, and ameliorated collagen-induced arthritis in DBA/1 mice. The ***Fas*** - ***ligand*** virus also inhibited production of interferon-gamma by collagen-specific T cells. Coadministration of Fas-immunoglobulin fusion protein with the ***Fas*** - ***ligand*** virus prevented these effects, demonstrating the specificity of the ***Fas*** - ***ligand*** virus. Thus, FasL gene transfer at the site of inflammation effectively ameliorates autoimmune disease.

L36 ANSWER 13 OF 19 BIOSIS COPYRIGHT 1998 BIOSIS
ACCESSION NUMBER: 97:280944 BIOSIS
DOCUMENT NUMBER: 99580147
TITLE: Functional analysis of a recombinant ***Fas*** ***ligand*** construct.
AUTHOR(S): Judge T A; Alonso L; Zhang H; Chen Y; Turka L A
CORPORATE SOURCE: Dep. Med., Univ. Pennsylvania, Philadelphia, PA 19104, USA
SOURCE: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association, Washington, D.C., USA, May 11-14, 1997. Gastroenterology 112 (4 SUPPL.). 1997. A1007. ISSN: 0016-5085
DOCUMENT TYPE: Conference
LANGUAGE: English

L36 ANSWER 14 OF 19 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97338658 MEDLINE
DOCUMENT NUMBER: 97338658
TITLE: ***Adenovirus*** -mediated expression of ***Fas*** ***ligand*** induces hepatic ***apoptosis*** after Systemic administration and ***apoptosis*** of ex vivo-infected pancreatic islet allografts and isografts.
AUTHOR: Muruve D A; Nicolson A G; Manfro R C; Strom T B; Sukhatme V P; Libermann T A
CORPORATE SOURCE: Division of Immunology, Beth Israel Deaconess Medical Center, Boston, MA, USA.
CONTRACT NUMBER: DK51060 (NIDDK)
SOURCE: HUMAN GENE THERAPY, (1997 May 20) 8 (8) 955-63. Journal code: A12. ISSN: 1043-0342.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY WEEK: 19971002
AB ***Fas*** ***ligand*** (FasL) mediates ***apoptosis*** of Fas-bearing cells and is expressed on a limited number of tissues, predominantly activated T lymphocytes. We describe the construction and biological activity of a replication-deficient type-5 ***adenovirus*** encoding murine FasL under the control of the cytomegalovirus (CMV) promoter (adCMV-FasL). In vitro, Jurkat cells undergo ***apoptosis*** when co-incubated with adCMV-FasL-infected COS cells. Systemic administration of adCMV-FasL to Wistar rats or DBA/2J mice results in widespread hepatic ***apoptosis*** and death in a dose-dependent manner within 72 hr, an effect not seen in lpr mice, or animals administered equivalent doses of adCMV-beta gal. Murine pancreatic islets also undergo ***apoptosis*** when infected ex vivo with adCMV-FasL, resulting in uniform primary nonfunction when transplanted into syngeneic or allogeneic diabetic recipients. These results indicate that adCMV-FasL is a potentially useful tool to study Fas/FasL biology.

L36 ANSWER 15 OF 19 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 97:497218 SCISEARCH
THE GENUINE ARTICLE: XG579
TITLE: ***Apoptosis*** signaling pathway in T cells is composed of ICE/Ced-3 family proteases and MAP kinase kinase 6b
AUTHOR: Huang S (Reprint); Jiang Y; Li Z J; Nishida E; Mathias P; Lin S C; Ulevitch R J; Nemerow G R; Han J H
CORPORATE SOURCE: SCRIPPS CLIN & RES INST, DEPT IMMUNOL, LA JOLLA, CA 92037 (Reprint); KYOTO UNIV, INST VIRUS RES, SAKYO KU, KYOTO 60601, JAPAN; NATL UNIV SINGAPORE, INST MOL & CELL BIOL, SINGAPORE 119260, SINGAPORE
COUNTRY OF AUTHOR: USA; JAPAN; SINGAPORE
SOURCE: IMMUNITY, (JUN 1997) Vol. 6, No. 6, pp. 739-749. Publisher: CELL PRESS, 1050 MASSACHUSETTES AVE, CIRCULATION DEPT, CAMBRIDGE, MA 02138. ISSN: 1074-7613.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 66
ABSTRACT IS AVAILABLE IN THE ALL AND 1ALL FORMATS
AB Fas/APO-1(CD95) ligation activates programmed cell death, a cellular process that plays an important role in the maturation of the host immune response. We show that activation of a specific MAP kinase kinase (MKK), MKK6b, is necessary and sufficient for Fas-induced ***apoptosis*** of Jurkat T cells. MKK6b activation occurs downstream of an interleukin-1 converting enzyme-like (ICE-like) protease(s), while execution of the apoptotic pathway by MKK6b requires both ICE- and CPP32-like proteases. Surprisingly, the p38 MAP kinase protein, a known substrate of MKK6b, does not participate in Fas/MKK6b-mediated ***apoptosis*** . These findings indicate a divergence of the MKK6b signaling pathways, one of which activates p38 and leads to regulation of gene expression, and one of which activates the ICE/Ced-3 family of proteases and leads to cell death. These studies represent a demonstration of an apoptotic pathway that is comprised of both the ICE/Ced-3 family of proteases and MAP kinase kinase 6.

L36 ANSWER 16 OF 19 BIOSIS COPYRIGHT 1998 BIOSIS
ACCESSION NUMBER: 98:158504 BIOSIS
DOCUMENT NUMBER: 01158504
TITLE: Amelioration of collagen-induced arthritis by CD95, (Apo-1- ***Fas***)- ***ligand*** gene transfer.
AUTHOR(S): Zhang H; Yang Y; Horton J L; Samoilova E B; Judge T A; Turku L A; Wilson J M; Chen Y
CORPORATE SOURCE: Dep. Mol. Cell. Eng., Univ. Pennsylvania Sch. Med., Philadelphia, PA 19104, USA
SOURCE: 61st National Scientific Meeting of the American College of Rheumatology and the 32nd National Scientific Meeting of the Association of Rheumatology Health Professionals, Washington, DC, USA, November 8-12, 1997. Arthritis & Rheumatism 40 (9 SUPPL.). 1997. S294. ISSN: 0004-3591
DOCUMENT TYPE: Conference
LANGUAGE: English

L36 ANSWER 17 OF 19 BIOSIS COPYRIGHT 1998 BIOSIS
ACCESSION NUMBER: 98:158280 BIOSIS
DOCUMENT NUMBER: 01158280
TITLE: ***FAS*** ***ligand*** ***adenovirus*** gene therapy prevents lymphoproliferative autoimmune disease in GLD-GLD mice.
AUTHOR(S): Zhang H-G; Zhou T; Curiel D T; Mountz J D
CORPORATE SOURCE: Univ. Alabama at Birmingham, Birmingham VAMC, Birmingham, AL 35294, USA
SOURCE: 61st National Scientific Meeting of the American College of Rheumatology and the 32nd National Scientific Meeting of the Association of Rheumatology Health Professionals, Washington, DC, USA, November 8-12, 1997. Arthritis & Rheumatism 40 (9 SUPPL.). 1997. S256. ISSN: 0004-3591
DOCUMENT TYPE: Conference
LANGUAGE: English

L36 ANSWER 18 OF 19 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97047773 MEDLINE
DOCUMENT NUMBER: 97047773
TITLE: ***Apoptosis*** signaling pathways in normal T cells: differential activity of Bcl-2 and IL-1beta-converting enzyme family protease inhibitors on glucocorticoid- and Fas-mediated cytotoxicity.
AUTHOR: Moreno M B; Memon S A; Zacharchuk C M
CORPORATE SOURCE: Laboratory of Immune Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: JOURNAL OF IMMUNOLOGY, (1996 Nov 1) 157 (9) 3845-9. Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199702
ENTRY WEEK: 19970204
AB Fas-mediated ***apoptosis*** plays an important role in regulating the immune response in peripheral T cells. Restimulation of T cell blasts up-regulates Fas and ***Fas*** ***ligand*** expression, with subsequent interaction leading to cell death. Overexpression of Bcl-2 in tumor cells blocks ***apoptosis*** induced by many stimuli, but inhibition of Fas-mediated killing has not been consistently observed. To examine the behavior of Bcl-2 in normal cells, T cell blasts were transiently transfected with Bcl-2 and related gene products to determine the effect on apoptotic signaling. Transient overexpression of Bcl-2 in mouse and human T cell blasts did not block Fas-mediated ***apoptosis*** , whereas etoposide- and glucocorticoid-induced cytotoxicity was potently inhibited. Expression of Bcl-xL and ***adenovirus*** E1B 19K did not interfere with anti-Fas killing. In contrast, interleukin-1beta-converting enzyme family protease inhibitors Ac-DEVD-CHO and CrmA blocked Fas-mediated ***apoptosis*** . These results suggest that peripheral T cells use distinct ***apoptosis*** signaling pathways with differential sensitivity to Bcl-2 and interleukin-1beta-converting enzyme family protease inhibitors. Since T cells normally express Bcl-2 and Bcl-xL following activation, their inability to block Fas-mediated ***apoptosis*** may allow for the elimination of self-reactive cells and the appropriate regulation of immune responses.

L36 ANSWER 19 OF 19 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95340546 EMBASE
TITLE: Bcl-2 blocks glucocorticoid- but not Fas- or activation-induced ***apoptosis*** in a T cell hybridoma.
AUTHOR: Memon S.A.; Moreno M.B.; Petrak D.; Zacharchuk C.M.
CORPORATE SOURCE: National Institutes of Health, Building 10, Bethesda, MD 20892-1152, United States
SOURCE: Journal of Immunology, (1995) 155/10 (4644-4652). ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Overexpression of Bcl-2 can prevent or markedly delay cell death induced by a variety of apoptotic stimuli. Although Fas and ***Fas*** ***ligand*** (FasL) interactions play a major role in the elimination of self-reactive T cells in the periphery,

inhibition of Fas-mediated killing by Bcl-2 has not been consistently observed. The mouse T hybridoma 2B4.11 (2B4) has been a useful model to study glucocorticoid- and activation-induced ***apoptosis*** , which is mediated through Fas and FasL. Using both stable transfectants and transient transfections, overexpression of Bcl-2 or Bcl-x(L) readily blocked glucocorticoid-induced but not activation-induced ***apoptosis*** of 2B4 cells. Bcl-2 expression did not inhibit Fas-mediated cytotoxicity triggered by cells expressing FasL or by the transient transfection of human Fas. Similarly, overexpression of Bcl-2 in the mouse T hybridoma A1.1 did not block activation-induced/Fas-mediated ***apoptosis*** . In Jurkat cells, however, expression of Bcl-2 partially inhibited anti-Fas-induced cell death. A Bcl- 2-related protein that can interfere with anti-Fas killing, the adenoviral E1B 19K, also did not block activation-induced/Fas-mediated ***apoptosis*** in 2B4 cells. In contrast, expression of CrmA, a cowpox virus protein that inhibits ICE-like protease activity, blocked activation-induced ***apoptosis*** in 2B4 cells but had little effect on Dex-mediated cytotoxicity. These results show that: 1) Bcl-2 can have strikingly different anti-cell death activity in the same cell depending upon the apoptotic stimulus, 2) distinct ***apoptosis*** signaling pathways may exist with differential sensitivity to Bcl-2 and ICE-like protease inhibitors.

=> s l1 and l6 and l9

L37 1 L1 AND L6 AND L9

=> d l37 ibib ab

L37 ANSWER 1 OF 1 USPATFULL
ACCESSION NUMBER: 1998:72713 USPATFULL
TITLE: Bax omega protein and methods
INVENTOR(S): Bitler, Catherine Mastroni, Menlo Park, CA, United States
Bowersox, Stephen Scott, Menlo Park, CA, United States
Crea, Roberto, San Mateo, CA, United States
Demo, Susan Dunham, San Francisco, CA, United States
Horne, William A., San Diego, CA, United States
Zhou, Mei, Palo Alto, CA, United States
PATENT ASSIGNEE(S): Neurex Corporation, Menlo Park, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5770690	980623
APPLICATION INFO.:	US 96-616732	960315 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 95-495042, filed on 27 Jun 1995, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Ketter, James
ASSISTANT EXAMINER: Yucel, Irem
LEGAL REPRESENTATIVE: Sholtz, Charles K.; Dehlinger, Peter J.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 3023
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Bax-.omega. polynucleotides and polypeptides, and compositions effective to hybridize to Bax-.omega. polynucleotides are disclosed. Also disclosed are methods for altering ***apoptosis*** in cells, for promoting cell survival and for identifying compounds capable of affecting the binding of Bax-.omega. to other proteins involved in ***apoptosis*** .

=> s l1 and l6 and l10

L38 292 L1 AND L6 AND L10

=> s l38 and l5

L39 41 L38 AND L5

=> dup rem

ENTER L# LIST OR (END):l39

PROCESSING COMPLETED FOR L39
L40 27 DUP REM L39 (14 DUPLICATES REMOVED)

=> d l40 1-27 ibib ab

L40 ANSWER 1 OF 27 USPATFULL
ACCESSION NUMBER: 1998:72713 USPATFULL
TITLE: Bax omega protein and methods
INVENTOR(S): Bitler, Catherine Mastroni, Menlo Park, CA, United States
Bowersox, Stephen Scott, Menlo Park, CA, United States
Crea, Roberto, San Mateo, CA, United States
Demo, Susan Dunham, San Francisco, CA, United States
Horne, William A., San Diego, CA, United States
Zhou, Mei, Palo Alto, CA, United States
PATENT ASSIGNEE(S): Neurex Corporation, Menlo Park, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5770690	980623
APPLICATION INFO.:	US 96-616732	960315 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 95-495042, filed on 27 Jun 1995, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Ketter, James
ASSISTANT EXAMINER: Yucel, Irem
LEGAL REPRESENTATIVE: Sholtz, Charles K.; Dehlinger, Peter J.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 15 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 3023
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Bax-.omega. polynucleotides and polypeptides, and compositions effective to hybridize to Bax-.omega. polynucleotides are disclosed. Also disclosed are methods for altering ***apoptosis*** in cells, for promoting cell survival and for identifying compounds capable of affecting the binding of Bax-.omega. to other proteins involved in ***apoptosis*** .

L40 ANSWER 2 OF 27 USPATFULL
ACCESSION NUMBER: 1998:72416 USPATFULL
TITLE: Tricyclic retinoids, methods for their production and use
INVENTOR(S): Hwang, Chan Kou, Boulder, CO, United States
White, Steven K., San Diego, CA, United States
Bennani, Youssef L., La Jolla, CA, United States
Canan Koch, Stacie S., San Diego, CA, United States
Badea, Beth Ann, San Diego, CA, United States
Hebert, Jonathan J., Mission Viejo, CA, United States
Farmer, Luc J., La Jolla, CA, United States
Nadzan, Alex M., San Diego, CA, United States
PATENT ASSIGNEE(S): Ligand Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5770383	980623
APPLICATION INFO.:	US 95-475397	950607 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 94-366630, filed on 9 Nov 1994, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Achutamurthy, Ponnathapura
LEGAL REPRESENTATIVE: Respess, William L.; Elmer, J. Scott
NUMBER OF CLAIMS: 39
EXEMPLARY CLAIM: 1
LINE COUNT: 4055
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Tricyclic retinoids having activity for retinoic acid receptors and/or retinoid X receptors are provided. Also provided are pharmaceutical compositions incorporating such tricyclic retinoid compounds and methods for their therapeutic use.

L40 ANSWER 3 OF 27 USPATFULL
ACCESSION NUMBER: 1998:72415 USPATFULL
TITLE: Tricyclic retinoids, methods for their production and use
INVENTOR(S): Hwang, Chan Kou, Boulder, CO, United States
White, Steven K., San Diego, CA, United States
Badea, Beth Ann, San Diego, CA, United States
Nadzan, Alex M., San Diego, CA, United States
PATENT ASSIGNEE(S): Ligand Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5770382	980623
APPLICATION INFO.:	US 95-475514	950607 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 94-366630, filed on 30 Dec 1994, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Achutamurthy, Ponnathapura
LEGAL REPRESENTATIVE: Respess, William L.; Elmer, J. Scott
NUMBER OF CLAIMS: 39
EXEMPLARY CLAIM: 1
LINE COUNT: 3975
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Tricyclic retinoids having activity for retinoic acid receptors and/or retinoid X receptors are provided. Also provided are pharmaceutical compositions incorporating such tricyclic retinoid compounds and methods for their therapeutic use.

L40 ANSWER 4 OF 27 USPATFULL
ACCESSION NUMBER: 1998:72412 USPATFULL
TITLE: Tricyclic retinoids, methods for their production and use
INVENTOR(S): Hwang, Chan Kou, Boulder, CO, United States
White, Steven K., San Diego, CA, United States
Bennani, Youssef L., La Jolla, CA, United States
Canan Koch, Stacie S., San Diego, CA, United States
Badea, Beth Ann, San Diego, CA, United States
Hebert, Jonathan J., Mission Viejo, CA, United States
Nadzan, Alex M., San Diego, CA, United States
PATENT ASSIGNEE(S): Ligand Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5770378	980623
APPLICATION INFO.:	US 95-472127	950607 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 94-366630, filed on 9 Nov 1994, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Achutamurthy, Ponnathapura
LEGAL REPRESENTATIVE: Respess, William L.; Elmer, J. Scott
NUMBER OF CLAIMS: 39
EXEMPLARY CLAIM: 1
LINE COUNT: 4031
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Tricyclic retinoids having activity for retinoic acid receptors and/or retinoid X receptors are provided. Also provided are pharmaceutical compositions incorporating such tricyclic retinoid compounds and methods for their therapeutic use.

L40 ANSWER 5 OF 27 USPATFULL
ACCESSION NUMBER: 1998:65012 USPATFULL
TITLE: DNA encoding a cytokine that induces ***apoptosis***
INVENTOR(S): Wiley, Steven R., Seattle, WA, United States

Goodwin, Raymond G., Seattle, WA, United States
PATENT ASSIGNEE(S): Immunex Corporation, Seattle, WA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5763223	980609
APPLICATION INFO.:	US 96-670354	960625 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 95-548368, filed on 1 Nov 1995, now abandoned which is a continuation-in-part of Ser. No. US 95-496632, filed on 29 Jun 1995, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Ulm, John
ASSISTANT EXAMINER: Mertz, Prema
LEGAL REPRESENTATIVE: Anderson, Kathryn A.
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 2248
AB A novel cytokine designated TRAIL induces ***apoptosis*** of certain target cells, including cancer cells and virally infected cells. Isolated DNA sequences encoding TRAIL are disclosed, along with expression vectors and transformed host cells useful in producing TRAIL polypeptides. Antibodies that specifically bind TRAIL are provided as well.

L40 ANSWER 6 OF 27 USPATFULL
ACCESSION NUMBER: 1998:65010 USPATFULL
TITLE: Human ***apoptosis*** -related calcium-binding protein
INVENTOR(S): Hillman, Jennifer L., San Jose, CA, United States
Goli, Surya K., Sunnyvale, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5763220	980609
APPLICATION INFO.:	US 96-766605	961212 (8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Wax, Robert A.
ASSISTANT EXAMINER: Bugaisky, Garbrile E.
LEGAL REPRESENTATIVE: Billings, Lucy J.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 2044
AB The present invention provides a human ***apoptosis*** -related calcium-binding protein (HARC) and polynucleotides which identify and encode HARC. The invention also provides genetically engineered expression vectors and host cells comprising the nucleic acid sequences encoding HARC and a method for producing HARC. The invention also provides for agonists, antibodies, or antagonists specifically binding HARC, and their use, in the prevention and treatment of diseases associated with expression of HARC. Additionally, the invention provides for the use of antisense molecules to polynucleotides encoding HARC for the treatment of diseases associated with the expression of HARC. The invention also provides diagnostic assays which utilize the polynucleotide, or fragments or the complement thereof, and antibodies specifically binding HARC.

L40 ANSWER 7 OF 27 USPATFULL
ACCESSION NUMBER: 1998:61156 USPATFULL
TITLE: Use of ***fas*** ***ligand*** to supress T-lymphocyte-mediated immune responses
INVENTOR(S): Bellgrau, Donald, Denver, CO, United States
Duke, Richard C., Denver, CO, United States
PATENT ASSIGNEE(S): University Technology Corporation, Boulder, CO, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5759536	980602
APPLICATION INFO.:	US 95-378507	950126 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 94-250478, filed on 27 May 1994, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Campbell, Bruce R.
LEGAL REPRESENTATIVE: Sheridan & Ross, P.C.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
LINE COUNT: 802
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for inhibiting T-lymphocyte-mediated immune responses, including those directed against autologous and/or heterologous tissues, e.g., by a recipient mammal of a transplanted tissue, said method comprising providing the recipient mammal with ***Fas*** ***ligand*** . The ***Fas*** ***ligand*** may be provided to the recipient mammal by a variety of means, including by pump implantation or by transplantation of transgenic tissue expressing ***Fas*** ***ligand*** . Also provided is a method for diagnostic use of ***Fas*** ***ligand*** expression in improving transplantation success.

L40 ANSWER 8 OF 27 USPATFULL
ACCESSION NUMBER: 1998:9346 USPATFULL
TITLE: Human cell death-associated protein
INVENTOR(S): Hawkins, Phillip R., Mountain View, CA, United States
Braxton, Scott Michael, San Mateo, CA, United States
Murry, Lynn E., Portola Valley, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5712115	980127
APPLICATION INFO.:	US 96-618164	960319 (8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Chan, Christina Y.
ASSISTANT EXAMINER: Cech, Emma
LEGAL REPRESENTATIVE: Incyte Pharmaceuticals, Inc.; Billings, Lucy J.; Luther, Barbara J.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1,2
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1765
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a polynucleotide which identifies and encodes a human cell death-associated protein (cdap) which was isolated from a rheumatoid synovium library. The invention provides for genetically engineered expression vectors and host cells comprising a nucleic acid sequence encoding CDAP. The invention also provides for the therapeutic use of purified CDAP, cdap or its antisense molecules, or CDAP inhibitors in pharmaceutical compositions and for treatment of conditions or diseases associated with expression of CDAP. The invention also describes diagnostic assays which utilize diagnostic compositions comprising the polynucleotide, or fragments thereof, or antibodies which specifically bind to the polypeptide.

L40 ANSWER 9 OF 27 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 1998:398802 SCISEARCH
THE GENUINE ARTICLE: ZN995
TITLE: The secreted hepatitis B precore antigen can modulate the immune response to the nucleocapsid: A mechanism for persistence
AUTHOR: Milich D R (Reprint); Chen M K; Hughes J L; Jones J E
CORPORATE SOURCE: SCRIPPS CLIN & RES INST, DEPT MOL BIOL, CAL-2, 10550 N TORREY PINES RD, LA JOLLA, CA 92037 (Reprint); KAROLINSKA INST, DIV CLIN VIROL, HUDDINGE, SWEDEN
COUNTRY OF AUTHOR: USA; SWEDEN
SOURCE: JOURNAL OF IMMUNOLOGY, (15 FEB 1998) Vol. 160, No. 4, pp. 2013-2021.
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0022-1767.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 54
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The hepatitis B precore Ag (HBeAg) is a secreted nonparticulate version of the ***viral*** nucleocapsid hepatitis B core Ag (HBcAg), and its function is unknown. A proportion of HBeAg-specific Th cells evade deletion/anergy in HBeAg-transgenic (Tg) mite and mediate anti-HBe "autoantibody" (autoAb) production after in vivo activation with the appropriate Th cell peptide, This model system was used to determine how secretory HBeAg may effect deletion of Th cells in the periphery. For this purpose, HBeAg-Tg mice were bred with Fas and ***Fas*** ***ligand*** (FasL)-defective lpr/lpr and gld/gld mutant mice. Fas-FasL interactions mediate activation-induced ***apoptosis*** in the periphery. In HBeAg-Tg/+ mice, high-titrated anti-HBe autoAb was produced that was exclusively composed of the IgG1 isotype (i.e., Th2-like profile), In contrast, HBeAg-Tg/lpr and HBeAg-Tg/gld mice produced significantly less anti-HBe autoAb, and the IgG isotype patterns were broadened to include IgG2a, IgG2b and IgG3 as wed as IgG1 (i.e., mixed Th1/Th2-like profile). These results suggest that HBeAg-specific Th1 cells are preferentially depleted by Fas-FasL-mediated interactions. The effect of circulating HBeAg on HBcAg-specific Th1 cells was also examined by transferring HBe/HBcAg-specific Th cells into dual HBeAg- and HBcAg-expressing Tg recipient mice. The presence of serum HBeAg ablated the expected Th1-mediated anti-HBc Ab response and shifted it toward a Th2 phenotype. These results suggest that in the context of a hepatitis B ***viral*** infection, circulating HBeAg has the potential to preferentially deplete inflammatory HBeAg- and HBcAg-specific Th1 cells that are necessary for ***viral*** clearance, thereby promoting hepatitis B ***virus*** persistence.

L40 ANSWER 10 OF 27 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998196839 EMBASE
TITLE: Self-veto mechanism of CD8+ cytotoxic effector T cells. Peptide-induced paralysis affects the peptide-MHC-recognizing cytotoxic T lymphocytes and is independent of Fas/ ***Fas*** ***ligand*** interactions.
AUTHOR: Bergenthal A.; Hofmann M.; Heeg K.
CORPORATE SOURCE: A. Bergenthal, Inst Med Microbiol Immunol Hygiene, Technical University of Munich, Trogerstr. 32, D-81675 Munich, Germany
SOURCE: European Journal of Immunology, (1998) 28/6 (1911-1922).
Refs: 46
ISSN: 0014-2980 CODEN: EJIMAF
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The lytic activity of CD8+ cytotoxic T lymphocyte (CTL) cell lines or clones can be inhibited by addition of the peptide recognized by these cells. The mechanisms underlying this phenomenon are not fully understood. Here we have analyzed peptide-induced CTL paralysis using in vivo generated ovalbumin (OVA)-specific CTL. Lytic activity of OVA-specific CTL was inhibited by addition of the immunodominant OVA-peptide SIINFEKL in a dose-dependent manner. Paralysis was induced rapidly and binding of the peptide to MHC class I molecules was required. Using mixing experiments with CTL populations of different peptide specificities restricted to the same MHC class I molecule we identified a veto-like mechanism: the cytotoxic activity of the peptide-recognizing CTL was inhibited while the lytic activity of the peptide-presenting CTL was unaltered. Only CD8+ CTL but not CD4+ T cells or B+ cells induced paralysis. After removal of the peptide-presenting CTL by magnetic cell sorting, paralysis was maintained and paralyzed CTL showed no signs of ***apoptosis*** . Loss of cytotoxicity could be induced in CTL populations from Fas-deficient (lpr+/lpr+) or ***Fas*** ***ligand*** -deficient (gld+/gld+) mice and mixtures thereof, implying that Fas/

Fas ***ligand*** interactions are not involved during induction of paralysis. Hence, peptide-induced paralysis of CTL is due to a self-veto mechanism rather than to mutual killing of CTL. These findings may have implications for in vivo immunization with peptides, ***viral*** escape and peripheral ***tolerance*** mechanisms.

L40 ANSWER 11 OF 27 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 98:273182 BIOSIS
DOCUMENT NUMBER: 01273182
TITLE: Fas antigen expression and ***apoptosis*** of lymphocytes in macaques infected with simian immunodeficiency ***virus*** strain mac.
AUTHOR(S): Iida T; Igarashi T; Ichimura H; Kuwata T; Shimada T; Nagamachi D; Yonehara S; Imanishi J; Hayami M
CORPORATE SOURCE: Dep. Microbiol., Kyoto Prefectural Univ. Med., Kyoto 602, Japan
SOURCE: Archives of Virology 143 (4). 1998. 717-729.
ISSN: 0304-8608
LANGUAGE: English
AB To investigate the role of ***apoptosis*** in the pathogenesis of HIV infection we used macaques infected with simian immunodeficiency ***virus*** (SIV) as a primate model and examined the characteristics of the ***apoptosis*** of lymphocytes in SIV mac-infected macaques. In vitro ***apoptosis*** was more strongly induced in peripheral blood mononuclear cells (PBMC) from SIV mac239-infected macaques than those from uninfected controls. We found that the frequency of Fas antigen-positive cells was higher in PBMC from SIV mac-infected macaques than from uninfected controls, and in vitro ***apoptosis*** of PBMC was ***suppressed*** by an inhibitor of the interleukin-1-beta converting enzyme (ICE) family proteases. In biopsied lymph nodes, the number of apoptotic nuclei in T cell-dependent areas was higher in SIVmac-infected macaques than in uninfected controls. A higher number of apoptotic nuclei in lymph nodes of SIVmac-infected macaques was observed in the stage of persistent general lymphadenopathy than in those with AIDS-related complex, while there was no significant difference in the extent of ***apoptosis*** of cultured PBMC among the SIVmac-infected macaques. These results suggest that in vitro ***apoptosis*** is mediated by the Fas/ ***Fas*** ***ligand*** and ICE system and that ***apoptosis*** in lymph nodes may be more closely related to the stage of SIVmac infection than is that of cultured PBMC.

L40 ANSWER 12 OF 27 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998037389 EMBASE
TITLE: ***Apoptosis*** in liver transplantation: A mechanism contributing to immune modulation, preservation injury, neoplasia, and ***viral*** disease.
AUTHOR: Patel T.; Gores G.J.
CORPORATE SOURCE: Dr. G.J. Gores, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States
SOURCE: Liver Transplantation and Surgery, (1998) 4/1 (42-50).
Refs: 55
ISSN: 1074-3022 CODEN: LTSUF3
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 009 Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although clinical liver transplantation has become a reality for the treatment of previously fatal end-stage chronic liver disease of fulminant hepatic failure, there are several limitations to its use. Allograft rejection is prevented only by induction of an artificial state of immunocompetence in the recipient by the use of nonspecific immunosuppression. This increases the risk of infection and malignancy. These complicating can be avoided only if ***tolerance*** to specific donor organ antigens is achieved and nonspecific immunosuppression is avoided. Understanding the role of ***apoptosis*** in the immune response to transplantation and study of the molecular and biochemical modulation of ***apoptosis*** may provide fertile ground for investigation relevant at liver transplantation. Such study may yield novel approaches to (1) the diagnosis, treatment, or prevention of rejection after transplantation; (2) therapeutic modulation of ***apoptosis*** in effector and target cells to limit immune-mediated damage; (3) rational immunosuppressive drug design; (4) strategies to allow development of graft ***tolerance*** , e.g., by selective deletion of antigen-specific T-cell populations; and (5) further avenues for research into the pathophysiology of conditions associated with transplantation such as malignancy, infection, preservation injury, and recurrent disease.

L40 ANSWER 13 OF 27 USPATFULL
ACCESSION NUMBER: 97:31611 USPATFULL
TITLE: Human anti-Fas IgG1 monoclonal antibodies
INVENTOR(S): Lynch, David H., Bainbridge Island, WA, United States
Alderson, Mark R., Bainbridge Island, WA, United States
PATENT ASSIGNEE(S): Immunex Corporation, Seattle, WA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5620889	970415
APPLICATION INFO.:	US 94-322805	941013 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 93-159003, filed on 29 Nov 1993, now abandoned which is a continuation-in-part of Ser. No. US 93-136817, filed on 14 Oct 1993, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Loring, Susan A.
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 1698
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a panel of monoclonal antibodies and binding proteins which specifically bind to human Fas antigen. Some of the antibodies and binding proteins are capable of stimulating T cell proliferation, inhibiting binding of anti-Fas CH-11 monoclonal antibody to cells expressing Fas antigen, blocking anti-Fas CH-11 monoclonal antibody-mediated lysis of cells, and blocking ***Fas*** ***ligand*** -mediated lysis of cells. The invention also provides for therapeutic compositions comprising the monoclonal antibodies.

L40 ANSWER 14 OF 27 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998004919 EMBASE
TITLE: Gene transfer of ***Fas*** ***ligand*** induces tumor regression in vivo.
AUTHOR: Arai H.; Gordon D.; Nabel E.G.; Nabel G.J.
CORPORATE SOURCE: G.J. Nabel, Howard Hughes Medical Institute, Univ. of Michigan Medical Center, West Medical Center Drive, Ann Arbor, MI 48109-0650, United States.
gnabel@umich.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1997) 94/25 (13862-13867).
Refs: 30
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The Fas- ***Fas*** ***ligand*** (FasL) system plays an important role in the induction of lymphoid ***apoptosis*** and has been implicated in the ***suppression*** of immune responses. Herein, we report that gene transfer of FasL inhibits tumor cell growth in vivo. Although such inhibition is expected in Fas+ tumor cell lines, marked regression was unexpectedly observed after FasL gene transfer into the CT26 colon carcinoma that does not express Fas. Infection by an adenoviral vector encoding FasL rapidly eliminated tumor masses in the Fas+ Renca tumor by inducing cell death, whereas the elimination of Fas- CT26 cells was mediated by inflammatory cells. Analysis of human malignancies revealed Fas, but not FasL, expression in a majority of tumors and susceptibility to FasL in most Fas+ cell lines. These findings suggest that gene transfer of FasL generates apoptotic responses and induces potent inflammatory reactions that can be used to induce the regression of malignancies.

L40 ANSWER 15 OF 27 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97161713 EMBASE
TITLE: CD2 rescues T cells from T-cell receptor/CD3 ***apoptosis*** : A role for the Fas/Fas-L system.
AUTHOR: Ayroldi E.; Migliorati G.; Cannarile L.; Moraca R.; Delfino D.V.; Riccardi C.
CORPORATE SOURCE: Dr. C. Riccardi, Section of Pharmacology, DCMPP, Via del Giochetto, 06100 Perugia, Italy
SOURCE: Blood, (1997) 89/10 (3717-3726).
Refs: 66
ISSN: 0006-4971 CODEN: BLOOAW
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 025 Hematology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Anti-CD3 monoclonal antibodies (MoAbs) and glucocorticoid hormones induce ***apoptosis*** in immature thymocytes end peripheral T lymphocytes. This process is inhibited by a number of growth factors, including interleukin-2 (IL-2), IL3, and IL-4, as well as by triggering of the adhesion molecule CD44, which would indicate that signals generated by membrane receptors can modulate the survival of lymphoid cells. To investigate whether triggering of CD2 may also affect ***apoptosis*** in lymphoid cells, we analyzed the effect of stimulation with anti-CD2 MoAbs on T-cell ***apoptosis*** induced by two stimuli, anti-CD3 MoAbs and dexamethasone (DEX), using a hybridoma T-cell line and a T-helper cell clone. The results show that CD2 engagement decreased anti-CD3 MoAb-induced ***apoptosis*** , but did not influence DEX-induced cell death. Furthermore, the decrease appeared to be related to the expression of Fas/APO-1 (CD95) and ***Fas*** - ***ligand*** (FasL). In fact, we show that CD2 stimulation inhibits ***apoptosis*** by preventing the CD3-induced upregulation of Fas and FasL in a Fas-dependent experimental system. These data suggest that a costimulatory molecule may control a deletion pathway and may therefore contribute to the regulation of peripheral ***tolerance*** .

L40 ANSWER 16 OF 27 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97474763 MEDLINE
DOCUMENT NUMBER: 97474763
TITLE: Amelioration of collagen-induced arthritis by CD95 (Apo-1/ ***Fas***)- ***ligand*** gene transfer.
AUTHOR: Zhang H; Yang Y; Horton J L; Samoilova E B; Judge T A; Turka L A; Wilson J M; Chen Y
CORPORATE SOURCE: Institute for Human Gene Therapy, Department of Molecular and Cellular Engineering, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1997 Oct 15) 100 (8) 1951-7.
Journal code: HS7. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104
AB Both rheumatoid arthritis and animal models of autoimmune arthritis are characterized by hyperactivation of synovial cells and hyperplasia of the synovial membrane. The activated synovial cells produce inflammatory cytokines and degradative enzymes that lead to destruction of cartilage and bones. Effective treatment of arthritis may require elimination of most or all activated synovial cells. The

death factor Fas/Apo-1 and its ligand (FasL) play pivotal roles in maintaining self- ***tolerance*** and immune privilege. Fas is expressed constitutively in most tissues, and is dramatically upregulated at the site of inflammation. In both rheumatoid arthritis and animal models of autoimmune arthritis, high levels of Fas are expressed on activated synovial cells and infiltrating leukocytes in the inflamed joints. Unlike Fas, however, the levels of FasL expressed in the arthritic joints are extremely low, and most activated synovial cells survive despite high levels of Fas expression. To upregulate FasL expression in the arthritic joints, we have generated a recombinant replication-defective adenovirus carrying FasL gene; injection of the FasL ***virus*** into inflamed joints conferred high levels of FasL expression, induced ***apoptosis*** of synovial cells, and ameliorated collagen-induced arthritis in DBA/1 mice. The ***Fas*** - ***ligand*** ***virus*** also inhibited production of interferon-gamma by collagen-specific T cells. Coadministration of Fas-immunoglobulin fusion protein with the ***Fas*** - ***ligand*** ***virus*** prevented these effects, demonstrating the specificity of the ***Fas*** - ***ligand*** ***virus*** . Thus, FasL gene transfer at the site of inflammation effectively ameliorates autoimmune disease.

L40 ANSWER 17 OF 27 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 97:561378 SCISEARCH
THE GENUINE ARTICLE: XL789
TITLE: ***Suppression*** of concanavalin A-induced hepatitis in IFN-gamma(-/-) mice, but not in TNF-alpha(-/-) mice - Role for IFN-gamma in activating ***apoptosis*** of hepatocytes
AUTHOR: Tagawa Y; Sekikawa K; Iwakura Y (Reprint)
CORPORATE SOURCE: UNIV TOKYO, INST MED SCI, LAB ANIM RES CTR, MINATO KU, 4-6-1 SHIROKANEDAI, TOKYO 108, JAPAN (Reprint); UNIV TOKYO, INST MED SCI, LAB ANIM RES CTR, MINATO KU, TOKYO 108, JAPAN; NATL INST ANIM HLTH, DEPT IMMUNOL, TSUKUBA, IBARAKI 305, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: JOURNAL OF IMMUNOLOGY, (1 AUG 1997) Vol. 159, No. 3, pp. 1418-1428.
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0022-1767.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 60
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Con A-induced hepatitis (Con A-hepatitis) is a hepatitis model in which hepatic injury is supposed to be caused by cytokines from activated T cells. To elucidate the pathogenesis of this disease, we analysed the roles of IFN-gamma and TNF-cu using deficient mice of these cytokines. Development of hepatitis was reduced significantly in IFN-gamma(-/-) mice, while susceptibility of TNF-alpha(-/-) mice was not changed, interestingly, apoptotic cell death was observed in the affected livers of control car TNF-alpha(-/-) mice, but not in those of IFN-gamma(-/-) mice, Fas mRNA expression was increased in the livers of hepatitis mice, but less abundantly in those of IFN-gamma(-/-) mice, Since ***apoptosis*** of liver cells was rarely observed in Con A-treated lpr/lpr mice, involvement of the Fas- ***Fas*** ***ligand*** system in this apoptotic process was suggested, These observations suggest that IFN-gamma plays a central role in Con A-hepatitis by activating Fas-induced ***apoptosis*** of liver cells.

L40 ANSWER 18 OF 27 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998024372 EMBASE
TITLE: Serpins and programmed cell death.
AUTHOR: Salvesen G.S.
CORPORATE SOURCE: G.S. Salvesen, Burnham Institute, 10901 North Torrey Pines Road, San Diego, CA 92037, United States
SOURCE: Advances in Experimental Medicine and Biology, (1997) 425/- (177-183).
Refs: 55
ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English

L40 ANSWER 19 OF 27 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 3
ACCESSION NUMBER: 97:66029 BIOSIS
DOCUMENT NUMBER: 99365232
TITLE: Cross-linking of Fas by antibodies to a peculiar domain of gp120 V3 loop can enhance T cell ***apoptosis*** in HIV-1-infected patients.
AUTHOR(S): Silvestris F; Nagata S; Cafforio P; Silvestris N; Dammacco F
CORPORATE SOURCE: DIMO, Sect. Intern. Med., P.za Giulio Cesare, 11, 70124 Bari, Italy
SOURCE: Journal of Experimental Medicine 184 (6). 1996. 2287-2300. ISSN: 0022-1007
LANGUAGE: English
AB Previous studies have demonstrated that T cell-reactive antibodies in HIV-1 infection contribute to lymphocyte depletion by cytotoxicity that involves differential membrane targets, such as the 43.5-kD receptor on CEM cells. Here, we show that these antibodies bind Fas as result of a molecular mimicry of the gp120. Both flow cytometry and immunoblotting using the human Fas-transfected mouse WC8 lymphoma revealed positive binding of immunoglobulin G from several patients to a 43.8-kD membrane receptor that also reacts with the CH11 anti-Fas monoclonal antibody. Specificity to Fas was further confirmed to chimeric recombinant human Fas-Fc by ELISA, whereas overlapping peptide mapping of a Fas domain (VEINCTR-N) shared by gp120 V3 loop demonstrated a predominant affinity to the full-length 10-mer peptide. Four anti-Fas affinity preparations greatly increased the subdiploid DNA peak of CEM cells similar to agonist ligands of Fas. In addition, anti-Fas immunoglobulin G strongly inhibited the (3H)thymidine uptake of CEM cells in proliferative assays, inducing a ***suppression*** as high as provoked by both CH11 mAb and recombinant human ***Fas*** ***ligand*** . Since anti-Fas were reactive to gp120, it is conceivable that antibodies binding that domain within the V3 region are effective cross-linkers of Fas and increase ***apoptosis*** in peripheral T cells. These results suggest that autologous stimulation of the Fas pathway, rather than of lymphocytotoxic antibodies, may aggravate lymphopenia in a number of HIV-1+ subjects.

L40 ANSWER 20 OF 27 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 4
ACCESSION NUMBER: 96:244888 BIOSIS
DOCUMENT NUMBER: 98793017
TITLE: Apoptotic depletion of CD4+ T cells in idiopathic CD4+ T lymphocytopenia.
AUTHOR(S): Laurence J; Mitra D; Steiner M; Lynch D H; Siegal F P; Staiano-Coico L
CORPORATE SOURCE: Cornell Univ. Med. Coll., 411 East 69th St., New York, NY 10021, USA
SOURCE: Journal of Clinical Investigation 97 (3). 1996. 672-680. ISSN: 0021-9738
LANGUAGE: English
AB Progressive loss of CD4+ T lymphocytes, accompanied by opportunistic infections characteristic of the acquired immune deficiency syndrome, has been reported in the absence of any known etiology. The pathogenesis of this syndrome, a subset of idiopathic CD4+ T lymphocytopenia (ICL), is uncertain. We report that CD4+ T cells from seven of eight ICL patients underwent accelerated programmed cell death, a process facilitated by T cell receptor cross-linking. ***Apoptosis*** was associated with enhanced expression of Fas and ***Fas*** ***ligand*** in unstimulated cell populations, and partially inhibited by soluble anti-Fas mAb. In addition, ***apoptosis*** was ***suppressed*** by aurintricarboxylic acid, an inhibitor of calcium-dependent endonucleases and proteases, in cells from four of seven patients. The in vivo significance of these findings was supported by three factors: the absence of accelerated ***apoptosis*** in persons with stable, physiologic CD4 lymphopenia without clinical immune deficiency; detection of serum antihistone H2B autoantibodies, one consequence of DNA fragmentation, in some patients; and its selectivity, with ***apoptosis*** limited to the CD4 population in some, and occurring among CD8 + T cells predominantly in those individuals with marked depletion of both CD4+ and CD8+ peripheral T lymphocyte subsets. These data suggest that patients with idiopathic loss of CD4+ T lymphocytes linked to clinical immune ***suppression*** have evidence for accelerated T cell ***apoptosis*** in vitro that may be pathophysiologic and amenable to therapy with ***apoptosis*** inhibitors.

L40 ANSWER 21 OF 27 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 96256141 MEDLINE
DOCUMENT NUMBER: 96256141
TITLE: HIV-1 upregulates ***Fas*** ***ligand*** expression in CD4+ T cells in vitro and in vivo: association with Fas-mediated ***apoptosis*** and modulation by aurintricarboxylic acid.
AUTHOR: Mitra D; Steiner M; Lynch D H; Staiano-Coico L; Laurence J
CORPORATE SOURCE: Laboratory for AIDS Virus Research, Cornell University Medical College, New York 10021, NY, USA.
CONTRACT NUMBER: RO1 HL5546 (NHLBI)
RO1 DE11348 (NIDR)
SOURCE: IMMUNOLOGY, (1996 Apr) 87 (4) 581-5.
Journal code: GH7. ISSN: 0019-2805.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199610
AB CD4+ T-lymphocyte ***apoptosis*** has been associated with human immunodeficiency ***virus*** (HIV)-1 infection in vitro, paralleling the expression of Fas (APO-1, CD95) on peripheral blood mononuclear cells from patients with HIV disease. However, the link between Fas induction, T-cell activation, and cell death is unclear. We document, for the first time, marked upregulation of expression of mRNA for the ligand for Fas in peripheral blood mononuclear cells from HIV seropositive individuals, and demonstrate the ability of HIV infection to induce such expression in CD4+ T cells in vitro. We also define the relevance of this expression to HIV-mediated CD4+ T cell death. Our ability to downregulate ***Fas*** ***ligand*** message and ***suppress*** HIV-mediated ***apoptosis*** with aurintricarboxylic acid, a clinically used protease inhibitor with known activity against programmed cell death in other systems, may open up a new area of therapy for HIV infection.

L40 ANSWER 22 OF 27 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 6
ACCESSION NUMBER: 96:157506 BIOSIS
DOCUMENT NUMBER: 98729641
TITLE: Overexpression of Fas antigen on T cells in advanced HIV-1 infection: Differential ligation constantly induces ***apoptosis*** .
AUTHOR(S): Silvestris F; Cafforio P; Frassanito M A; Tucci M; Romito A; Nagata S; Dammacco F
CORPORATE SOURCE: Dep. Biomedical Sciences Human Oncology, Section Internal Med., Univ. Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy
SOURCE: AIDS (Philadelphia) 10 (2). 1996. 131-141. ISSN: 0269-9370
LANGUAGE: English
AB Objectives: To investigate Fas in peripheral lymphocytes from HIV-1-positive patients at different disease stages with respect to the extent of ***apoptosis*** . Design: The study included analysis of Fas involvement in T-cell ***apoptosis*** observed during HIV-1 infection. Because ligation of Fas can result in costimulation of proliferation or the induction of ***apoptosis*** in uninfected cells, we evaluated the effect on T cells of Fas activation by monoclonal antibodies (MAb) of different specificity from both UB2 and CH11 clones and activation by the ***Fas*** ***ligand*** (Fas-L). Methods: Fas was measured by FACS in peripheral blood and in phytohaemagglutinin (PHA)-driven cultures derived from 59 HIV-1-positive individuals with different Centers for Disease Control and Prevention stages. The percentage of apoptotic cells was detected by propidium iodide cell staining. The effect of Fas ligation was assessed in peripheral T cells from patients and healthy controls by a proliferative test measuring the 3H-thymidine uptake. Results: FACS analysis revealed that Fas was predominantly expressed in advanced disease, although it was promptly exposed in

PHA cultures from asymptomatic individuals. In several instances, Fas overexpression was associated with substantial subdiploid DNA content in cells from severely lymphopenic patients. The proliferative assay showed a significant inhibition of 3H-thymidine uptake in T cells from all patients following Fas ligation by the immunoglobulin (Ig) G1 MAb from the UB2 clone. This was in contrast to the apparent cell activation detected in controls and the weak ***suppression*** observed in Fas-positive cell lines. In addition, the IgM anti-Fas and recombinant Fas-L concentrations inducing a moderate inhibition of fresh T cells from controls strongly depressed the proliferative rate of cells from patients. Conclusions: Our data suggest that Fas overexpression parallels the progression of the disease and that the increased susceptibility of T cells from HIV-1-infected individuals to undergo ***apoptosis*** may include a Fas pathway. Functionally exhausted T cells in advanced HIV-1 infection are primed to ***apoptosis*** because of their high sensitivity to Fas stimulation even using the IgG1 MAb, which is unreactive to the death domain of Fas. This suggests that the increased sensitivity of Fas is apparently unrelated to its trimeric ligation and supports the hypothesis that Fas pathway plays a role in increasing the lymphocyte ***apoptosis*** during the disease.

L40 ANSWER 23 OF 27 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 96:573933 SCISEARCH
THE GENUINE ARTICLE: UZ454
TITLE: CD95-INDUCED ***APOPTOSIS*** OF LYMPHOCYTES IN AN IMMUNE PRIVILEGED SITE INDUCES IMMUNOLOGICAL-***TOLERANCE***
AUTHOR: GRIFFITH T S (Reprint); YU X H; HERNDON J M; GREEN D R; FERGUSON T A
CORPORATE SOURCE: WASHINGTON UNIV, SCH MED, DEPT OPHTHALMOL & VISUAL
SCI, ST LOUIS, MO, 63110 (Reprint); WASHINGTON UNIV, SCH MED, DEPT PATHOL, ST LOUIS, MO, 63110; LA JOLLA INST ALLERGY & IMMUNOL, DIV CELLULAR IMMUNOL, LA JOLLA, CA, 92037
COUNTRY OF AUTHOR: USA
SOURCE: IMMUNITY, (JUL 1996) Vol. 5, No. 1, pp. 7-16.
ISSN: 1074-7613.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 39
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB We examined the relationship between cell death and ***tolerance*** induction following antigen injection into the anterior chamber of the eye. Our data show that when inflammatory cells undergo ***apoptosis*** following infection with HSV-1, ***tolerance*** to the ***virus*** was observed. In contrast, when cell death was absent due to defects in Fas or FasL, immune ***tolerance*** was not observed. Further studies revealed that cell death and ***tolerance*** required that the lymphoid cells be Fas(+) and the eye be FasL(+). Additionally, we show that while Fas/FasL-mediated ***apoptosis*** occurred in the eye, it was apoptotic cell death that was critical for ***tolerance*** induction. Our results further demonstrate immune privilege is not a passive process involving physical barriers, but is an active process that employs an important natural mechanism to induce cell death and immune ***tolerance*** .

L40 ANSWER 24 OF 27 MEDLINE
ACCESSION NUMBER: 96062057 MEDLINE
DOCUMENT NUMBER: 96062057
TITLE: Clonal deletion of major histocompatibility complex class I-restricted CD4+CD8+ thymocytes in vitro is independent of the CD95 (APO-1/ ***Fas***) ***ligand*** .
AUTHOR: Muller K P; Mariani S M; Matiba B; Kyewski B; Krammer P H
CORPORATE SOURCE: Tumor Immunology Program, German Cancer Research Center, Heidelberg, Germany.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Oct) 25 (10) 2996-9.
Journal code: EN5. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199602
AB The CD95 (APO-1/ ***Fas***) ***ligand*** (CD95L) mediates ***apoptosis*** in sensitive target cells, Ca(2+)-independent cytotoxicity of cells from perforin knock-out mice, and peripheral deletion of activated T cells through engagement of its cognate receptor CD95. Double-positive thymocytes show a high constitutive expression of CD95. Therefore, we used a model system and investigated whether negative selection through ***apoptosis*** might involve CD95/CD95L. We analyzed whether CD95L may induce antigen-specific deletion of double-positive thymocytes from mice transgenic for a lymphocytic choriomeningitis ***virus*** (LCMV)/H2b-specific T cell receptor (TCR). These cells are deleted in vitro upon addition of the LCMV-peptide 33-41 in a major histocompatibility complex-class I-restricted fashion. Deletion was not blocked by soluble mouse and human CD95-Fc receptor decoys. CD95-Fc receptor decoys, however, were effective in blocking ***apoptosis*** induced by mouse CD95L-transfected L929 cells in sensitive CD95+ target cells and in thymocytes. These results suggest that TCR-induced deletion of immature thymocytes in vitro is independent of CD95L. Thus, our data argue against a role of CD95L in negative selection of MHC-class I-restricted autoreactive thymocytes.

L40 ANSWER 25 OF 27 MEDLINE
ACCESSION NUMBER: 96072969 MEDLINE
DOCUMENT NUMBER: 96072969
TITLE: ***Fas*** ***ligand*** -induced ***apoptosis*** as a mechanism of immune privilege [see comments].
COMMENT: Comment in: Science 1995 Nov 17;270(5239):1158-9
AUTHOR: Griffith T S; Brunner T; Fletcher S M; Green D R; Ferguson T A
CORPORATE SOURCE: Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, MO 63110, USA.
CONTRACT NUMBER: EY06765 (NEI)
EY02687 (NEI)
SOURCE: SCIENCE, (1995 Nov 17) 270 (5239) 1189-92.
Journal code: UJ7. ISSN: 0036-8075.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199603
AB The eye is a privileged site that cannot tolerate destructive inflammatory responses. Inflammatory cells entering the anterior chamber of the eye in response to ***viral*** infection underwent ***apoptosis*** that was dependent on Fas (CD95)-***Fas*** ***ligand*** (FasL) and produced no tissue damage. In contrast, ***viral*** infection in gld mice, which lack functional FasL, resulted in an inflammation and invasion of ocular tissue without ***apoptosis*** . Fas-positive but not Fas-negative tumor cells were killed by ***apoptosis*** when placed within isolated anterior segments of the eyes of normal but not FasL-negative mice. FasL messenger RNA and protein were detectable in the eye. Thus, Fas-FasL interactions appear to be an important mechanism for the maintenance of immune privilege.

L40 ANSWER 26 OF 27 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 96070657 MEDLINE
DOCUMENT NUMBER: 96070657
TITLE: Increased expression of Fas antigen on bone marrow CD34+ cells of patients with aplastic anaemia.
AUTHOR: Maciejewski J P; Selleri C; Sato T; Anderson S; Young N S
CORPORATE SOURCE: Hematology Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892-1652, USA..
SOURCE: BRITISH JOURNAL OF HAEMATOLOGY, (1995 Sep) 91 (1) 245-52.
Journal code: AXC. ISSN: 0007-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199602
AB Fas antigen, a receptor molecule that mediates signals for programmed cell death, is involved in T-cell-mediated killing of malignant, ***virus*** -infected or allogeneic target cells. Interferon-gamma (IFN-gamma) and tumour necrosis factor-alpha (TNF-alpha), potent inhibitors of haemopoiesis, enhance Fas receptor expression on bone marrow (BM) CD34+ cells, and both cytokines render haemopoietic progenitor cells susceptible to Fas-mediated inhibition of colony formation due to the induction of ***apoptosis*** . Haemopoietic ***suppression*** in aplastic anaemia (AA) has been associated with aberrant IFN-gamma, increased TNF-beta expression, and elevated numbers of activated cytotoxic T-cells in marrow. We have now examined Fas antigen expression in fresh AA BM samples. In normal individuals few CD34+ cells expressed Fas antigen and normal marrow cells had low sensitivity to Fas-mediated inhibition of colony formation. In contrast, in early AA, BM CD34+ cells showed markedly increased percentages of Fas receptor-expressing CD34+ cells, which correlated with increased sensitivity of AA marrow cells to anti-Fas antibody-mediated inhibition of colony formation. The proportion of Fas antigen-bearing cells was lower in recovered patients' BM. Fas antigen was also detected in the marrow of some patients with myelodysplasia, especially the hypocellular variant. These results are consistent with the hypothesis that AA CD34+ cells, probably including haemopoietic progenitor cells, express high levels of Fas receptor due to in vivo exposure to IFN-gamma and/or TNF-alpha and are suitable targets for T-cell-mediated killing. Our results suggest that the Fas receptor/ ***Fas*** ***ligand*** system are involved in the pathophysiology of BM failure.

L40 ANSWER 27 OF 27 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95211297 EMBASE
TITLE: Autoimmunity, ***apoptosis*** defects and retroviruses.
AUTHOR: Mountz J.D.; Cheng J.; Su X.; Wu J.; Zhou T.
CORPORATE SOURCE: Department of Medicine, Birmingham Veterans Admin. Med. Ctr., University of Alabama, Birmingham, AL 35294-0007, United States
SOURCE: Advances in Experimental Medicine and Biology, (1995) 374/- (183-201).
ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Autoimmune disease in both mice and humans is associated with increased expression of endogenous retroviruses in the thymus and T cells, and loss of self- ***tolerance*** by T cells. The basic genetic defect underlying autoimmune disease has been identified as a mutation of the Fas ***apoptosis*** antigen in MRL-lpr/lpr mice or a mutation of the ***Fas*** ***ligand*** in C3H-gld/gld mice. In MRL- lpr/lpr mice, the lpr mutation results from a 5.3 kb insertion of the ETn retrotransposon in the second intron of the Fas gene. In contrast to normal mice, which express a 2.2 kb normal size Fas cDNA, MRL-lpr/lpr mice express multiple Fas RNA transcripts ranging from 2-10.5 kb. In addition, a 5.7 kb full-length ETn transcript is highly expressed in the thymus of younger MRL- lpr/lpr mice. To determine if high ETn expression was dependent on abnormal Fas expression, CD2-fas transgenic mice were produced using the full-length murine Fas cDNA under the regulation of the CD2 promoter and enhancer. This resulted in normalization of Fas expression and also elimination of expression of the ETn retrotransposon. The ETn regulatory sequence contains potential DNA binding sites found in the enhancers of many genes activated during early T cell development in the thymus including enhancer regions for the TCR, CD3 and IL-2 genes. Therefore we propose that ETn expression is increased during early T cell development in the thymus, or after T cell activation, and that the integration of ETn in the Fas ***apoptosis*** gene leads to abnormal T cell

apoptosis or development. Human autoimmune disease has also been found to result from production of a soluble inhibitor of ***apoptosis*** . The full-length cDNA and genomic clones for human Fas were cloned and sequenced. Patients with SLE produced high levels of an alternatively spliced soluble Fas (sFas) RNA lacking the transmembrane (exon 6) resulting in high circulating levels of the Fas molecule. This human sFas molecule was able to inhibit ***apoptosis*** in vitro at levels found in serum of SLE patients (200 ng/ml): The same levels of mouse sFas were able to inhibit ***apoptosis*** in vivo in mice resulting in a 3-fold increase in spleen size, and altered thymocyte maturation consisting of increased production of CD4-CD8- T cells and decreased CD4+CD8+ T cells. Regulation of Fas signaling in human T cells also plays a role in abnormal ***apoptosis*** . Fas signaling is mediated by the hematopoietic stem cell phosphatase, (Hcph) and is inhibited in the Hcph deficient Molt-4 T cell, the phosphatase deficient motheaten (me/me) mice and by the tyrosine phosphatase inhibitor pervanadate. Multiple pathways of Fas ***apoptosis*** were also shown to exist, as Fas induced ***apoptosis*** is increased in the liver of me/me mice, and signaling likely also involves an sphingomylinase-ceramide activated kinase pathway as utilized by the TNF-R. ***Fas*** ***ligand*** has been recently cloned in mice and humans, and is homologous to TNF-.alpha.. The ***Fas*** ***ligand*** defect in autoimmune C3H-gld/gld mice is due to a point mutation resulting in a single amino acid change in the hydrophobic region of the ***Fas*** ***ligand*** trimer. These results indicate that T cell ***apoptosis*** can be dramatically increased or decreased by cellular interactions which in turn regulate either the levels of production or signaling activity of the Fas and ***Fas*** ***ligand*** . Retroviruses and their products can influence ***apoptosis*** by altering expression of Fas or Fas-L, or altering apoptotic signaling after Fas/Fas-L interactions. Further insights into the regulation of ***apoptosis*** molecules will be important in normalizing this activity when it is decreased as in the case of autoimmune disease, or when it is in excess, as is the case with HIV disease.

=> s l1 and l6 and l12

L41 3 L1 AND L6 AND L12

=> dup rem

ENTER L# LIST OR (END):l41

L42 3 DUP REM L41 (0 DUPLICATES REMOVED)

=> d l42 1-3 ibib ab

L42 ANSWER 1 OF 3 BIOSIS COPYRIGHT 1998 BIOSIS
ACCESSION NUMBER: 98:228880 BIOSIS
DOCUMENT NUMBER: 01228880
TITLE: Immunopathology of Sjogren's syndrome.
AUTHOR(S): Tapinos N I; Polihronis M; Tzioufas A G; Skopouli F N
CORPORATE SOURCE: Dep. Pathophysiol., Sch. Med., Univ. Athens, M. Asias 75, Goudi, 115 27 Athens, Greece
SOURCE: Annales de Medecine Interne 149 (1). 1998. 17-24. ISSN: 0003-410X
LANGUAGE: English
AB Sjogren's syndrome is a chronic autoimmune disorder characterized by mononuclear cell infiltration around epithelial cells of exocrine glands. In recent years, several studies have tried to elucidate the components of the immunopathologic interaction in Sjogren's syndrome as well as the function of these components. The majority of the mononuclear infiltrating cells are CD4 positive T lymphocytes (60-70%) whereas B cells constitute one fourth of the infiltrating cells. Macrophages and natural killer cells are poorly represented in the lesion. Epithelial cells of minor salivary glands of patients with Sjogren's syndrome express several cytokines (IL-1-beta, IL-6, NO), protooncogenes (c-myc), autoantigens (Ro, La, Fodrin) and costimulatory molecules (B71, B72). The characteristic destruction of epithelial cells of Sjogren's syndrome patients is probably due to activation of several apoptotic pathways since epithelial cells express different ***apoptosis*** related molecules such as Fas, FasL, Bax, while mononuclear cells express Perforin and Granzymes. Finally epithelial cells seem to exert a regenerative effort since they express trefoil proteins (pS2). The above mentioned properties give epithelial cells the leading role in the pathophysiology of the syndrome but the exact causative agent which drives the immune system towards an autoimmune reaction still remains obscure.

L42 ANSWER 2 OF 3 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 95:471454 SCISEARCH
THE GENUINE ARTICLE: RJ028
TITLE: CD95 (FAS) DEPENDENT ELIMINATION OF SELF-REACTIVE B-CELLS UPON INTERACTION WITH CD4(+) T-CELLS
AUTHOR: RATHMELL J C (Reprint); COOKE M P; HO W Y; GREIN J; TOWNSEND S E; DAVIS M M; GOODNOW C C
CORPORATE SOURCE: STANFORD UNIV, SCH MED, HOWARD HUGHES MED INST, STANFORD, CA, 94305 (Reprint); STANFORD UNIV, SCH MED, PROGRAM IMMUNOL, STANFORD, CA, 94305; STANFORD UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, STANFORD, CA, 94305
COUNTRY OF AUTHOR: USA
SOURCE: NATURE, (13 JUL 1995) Vol. 376, No. 6536, pp. 181-184. ISSN: 0028-0836.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS; LIFE; AGRI
LANGUAGE: ENGLISH
REFERENCE COUNT: 29
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB THE recessive mouse mutations lpr and gld create deficiencies in an interacting pair of cell surface molecules, CD95 (Fas/APO-1) and ***Fas*** , ***ligand*** (FasL), respectively(1-3), resulting in autoantibody production resembling human systemic lupus erythematosus(4). The mechanisms of self-tolerance affected by deficiency in either molecule are not established, but CD95 deficiency both in B cells and in CD4(+) T cells recognizing major histocompatibility complex (MHC) class II molecules is required for autoimmunity in lpr mice(5-8). Here we track the outcome of in vivo interactions between B cells and CD4(+) T cells that recognize a transgene-encoded ***autoantigen*** , hen egg lysozyme (HEL), using cells from mice transgenic for immunoglobulin and T-cell receptor (TCR) genes. B cells that had not previously encountered HEL ***autoantigen*** (naive cells) were triggered into proliferation and antibody-production upon interaction with antigen and HEL-specific CD4(+) T cells. By contrast, B cells that had been chronically exposed to HEL during their development and carried desensitized surface immunoglobulin (sIg) antigen receptors(9) (anergic cells) did not produce antibody but instead were eliminated in the presence of HEL-specific CD4(+) T cells. CD95-deficient anergic B cells, however, were not eliminated by CD4(+) T cells and were triggered to proliferate. These findings identify a novel regulatory step for eliminating autoreactive B cells that seems unique in its dependence on CD95.

L42 ANSWER 3 OF 3 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95026707 EMBASE
TITLE: ***Apoptosis*** , fas and systemic autoimmunity: The MRL-lpr/lpr model.
AUTHOR: Singer G.G.; Carrera A.C.; Marshak-Rothstein A.; Martinez-A C.; Abbas A.K.
CORPORATE SOURCE: Immunology Research Division, Department of Pathology, Brigham and Women's Hospital, Boston, MA 02115, United States
SOURCE: Current Opinion in Immunology, (1994) 6/6 (913-920). ISSN: 0952-7915 CODEN: COPIEL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal
FILE SEGMENT: 022 Human Genetics
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Proteins encoded by the fas and ***fas*** ***ligand*** (fasL) genes are involved in apoptotic cell death in lymphocytes. In this article we review the recent elucidation of the role of the Fas-FasL interactions in the maintenance of tolerance to self antigens and in the homeostatic regulation of lymphocyte clonal expansion, and discuss the mechanisms of autoimmunity in Fas- and FasL-deficient mutant mouse strains.

=> s l1 and l6 and l13

L43 286 L1 AND L6 AND L13

=> s l1 and l6 and l13 and l5

L44 52 L1 AND L6 AND L13 AND L5

=> dup rem

ENTER L# LIST OR (END):l44

L45 31 DUP REM L44 (21 DUPLICATES REMOVED)

=> d l45 1-31 ibib ab

L45 ANSWER 1 OF 31 USPATFULL
ACCESSION NUMBER: 1998:65012 USPATFULL
TITLE: DNA encoding a cytokine that induces ***apoptosis***
INVENTOR(S): Wiley, Steven R., Seattle, WA, United States
Goodwin, Raymond G., Seattle, WA, United States
PATENT ASSIGNEE(S): Immunex Corporation, Seattle, WA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5763223	980609
APPLICATION INFO.:	US 96-670354	960625 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 95-548368, filed on 1 Nov 1995, now abandoned which is a continuation-in-part of Ser. No. US 95-496632, filed on 29 Jun 1995, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Ulm, John
ASSISTANT EXAMINER: Mertz, Prema
LEGAL REPRESENTATIVE: Anderson, Kathryn A.
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 2248
AB A novel cytokine designated TRAIL induces ***apoptosis*** of certain target cells, including cancer cells and virally infected cells. Isolated DNA sequences encoding TRAIL are disclosed, along with expression vectors and transformed host cells useful in producing TRAIL polypeptides. Antibodies that specifically bind TRAIL are provided as well.

L45 ANSWER 2 OF 31 USPATFULL
ACCESSION NUMBER: 1998:65010 USPATFULL
TITLE: Human ***apoptosis*** -related calcium-binding protein
INVENTOR(S): Hillman, Jennifer L., San Jose, CA, United States
Goli, Surya K., Sunnyvale, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5763220	980609
APPLICATION INFO.:	US 96-766605	961212 (8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Wax, Robert A.
ASSISTANT EXAMINER: Bugaisky, Garbrile E.
LEGAL REPRESENTATIVE: Billings, Lucy J.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 2044
AB The present invention provides a human ***apoptosis*** -related calcium-binding protein (HARC) and polynucleotides which identify

and encode HARC. The invention also provides genetically engineered expression vectors and host cells comprising the nucleic acid sequences encoding HARC and a method for producing HARC. The invention also provides for agonists, antibodies, or antagonists specifically binding HARC, and their use, in the prevention and treatment of diseases associated with expression of HARC. Additionally, the invention provides for the use of antisense molecules to polynucleotides encoding HARC for the treatment of diseases associated with the expression of HARC. The invention also provides diagnostic assays which utilize the polynucleotide, or fragments or the complement thereof, and antibodies specifically binding HARC.

L45 ANSWER 3 OF 31 USPATFULL
ACCESSION NUMBER: 1998:61156 USPATFULL
TITLE: Use of ***fas*** ***ligand*** to supress T-lymphocyte-mediated immune responses
INVENTOR(S): Bellgrau, Donald, Denver, CO, United States
Duke, Richard C., Denver, CO, United States
PATENT ASSIGNEE(S): University Technology Corporation, Boulder, CO, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5759536	980602
APPLICATION INFO.:	US 95-378507	950126 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 94-250478, filed on 27 May 1994, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Campbell, Bruce R.
LEGAL REPRESENTATIVE: Sheridan & Ross, P.C.
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
LINE COUNT: 802
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for inhibiting T-lymphocyte-mediated immune responses, including those directed against autologous and/or heterologous tissues, e.g., by a recipient mammal of a transplanted tissue, said method comprising providing the recipient mammal with ***Fas*** ***ligand*** . The ***Fas*** ***ligand*** may be provided to the recipient mammal by a variety of means, including by pump implantation or by transplantation of transgenic tissue expressing ***Fas*** ***ligand*** . Also provided is a method for diagnostic use of ***Fas*** ***ligand*** expression in improving transplantation success.

L45 ANSWER 4 OF 31 USPATFULL
ACCESSION NUMBER: 1998:9346 USPATFULL
TITLE: Human cell death-associated protein
INVENTOR(S): Hawkins, Phillip R., Mountain View, CA, United States
Braxton, Scott Michael, San Mateo, CA, United States
Murry, Lynn E., Portola Valley, CA, United States
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5712115	980127
APPLICATION INFO.:	US 96-618164	960319 (8)

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Chan, Christina Y.
ASSISTANT EXAMINER: Cech, Emma
LEGAL REPRESENTATIVE: Incyte Pharmaceuticals, Inc.; Billings, Lucy J.; Luther, Barbara J.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1,2
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1765
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a polynucleotide which identifies and encodes a human cell death-associated protein (cdap) which was isolated from a rheumatoid synovium library. The invention provides for genetically engineered expression vectors and host cells comprising a nucleic acid sequence encoding CDAP. The invention also provides for the therapeutic use of purified CDAP, cdap or its antisense molecules, or CDAP inhibitors in pharmaceutical compositions and for treatment of conditions or diseases associated with expression of CDAP. The invention also describes diagnostic assays which utilize diagnostic compositions comprising the polynucleotide, or fragments thereof, or antibodies which specifically bind to the polypeptide.

L45 ANSWER 5 OF 31 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 1998:138882 SCISEARCH
THE GENUINE ARTICLE: YW210
TITLE: Inhibition of Fas/ ***Fas*** ***ligand*** -mediated apoptotic cell death of lymphocytes in vitro by circulating anti- ***Fas*** ***ligand*** autoantibodies in patients with systemic lupus erythematosus
AUTHOR: Suzuki N (Reprint); Ichino M; Mihara S; Kaneko S; Sakane T
CORPORATE SOURCE: ST MARIANNA UNIV, SCH MED, DEPT IMMUNOL, MIYAMAE KU,
2-16-1 SUGAO, KANAGAWA 216, JAPAN (Reprint); ST MARIANNA UNIV, SCH MED, DEPT MED, MIYAMAE KU, KANAGAWA 216, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: ARTHRITIS AND RHEUMATISM, (FEB 1998) Vol. 41, No. 2, pp. 344-353.
Publisher: LIPPINCOTT-RAVEN PUBL, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106.
ISSN: 0004-3591.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 54
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Objective. The Fas/ ***Fas*** ***ligand*** (FasL) system has been assigned a pivotal role in the establishment and maintenance of peripheral ***tolerance*** , and mice having defects in the Fas/FasL system are known to develop lupus-like symptoms. However, it remains unclear whether the Fas/FasL system is involved in the pathogenesis of systemic lupus erythematosus (SLE) in humans. This study examined whether there are circulating anti-FasL autoantibodies in the peripheral blood of patients with SLE that would interfere with Fas/FasL-mediated ***apoptosis*** .
Methods. Anti-FasL autoantibodies were detected by Western blot analysis using the recombinant extracellular domain of human FasL as the antigen. ***Apoptosis*** of Fas-expressing Jurkat cells, induced by recombinant soluble FasL (sFasL) in the presence of anti-FasL autoantibodies, was assessed by DNA staining with propidium iodide, followed by flow cytometric analysis. ***Apoptosis*** of Jurkat cells by cell-bound FasL was assessed by 2-color analysis, involving TUNEL staining with fluorescein isothiocyanate-dUTP and phycoerythrin-labeled anti-CD3 monoclonal antibodies.
Results. Among the 21 patients with SLE, 7 had IgG-isotype anti-FasL autoantibodies in their circulating blood. In addition, these autoantibodies inhibited both sFasL-mediated and cell-bound FasL-mediated ***apoptosis*** of Fas-expressing Jurkat cells. Thus, it is plausible that anti-FasL autoantibodies in patients with SLE disturb the establishment and maintenance of peripheral ***tolerance*** in vivo by inhibiting the Fas/FasL-mediated elimination of autoreactive lymphocytes.
Conclusion. These results suggest that anti-FasL autoantibodies that inhibit Fas/FasL-mediated ***apoptosis*** are involved, at least in part, in immune abnormalities and may possibly be involved in the pathogenesis of SLE.

L45 ANSWER 6 OF 31 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998173681 EMBASE
TITLE: [The role of ***apoptosis*** in physiological and pathological processes].
AZ APOPTOZIS FIZIOLOGIAS ES PATOLOGIAS KORULMENYEK KOZOTT.
AUTHOR: Lakos G.; Szegedi G.
CORPORATE SOURCE: Dr. G. Lakos, Univ. Medical School of Debrecen, 3rd Department of Medicine, Moricz Zs. krt. 22, H-4004 Debrecen, Hungary
SOURCE: Lege Artis Medicine, (1998) 8/4 (246-253).
Refs: 51
ISSN: 0866-4811 CODEN: LAMEFU
COUNTRY: Hungary
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LANGUAGE: Hungarian
SUMMARY LANGUAGE: English; Hungarian
AB ***Apoptosis*** (programmed cell death) is the physiological way of the elimination of unnecessary cells from the organism, that is distinguished with characteristic features from necrosis. Cleavage of the DNA by endogenous endonuclease(s) is the hallmark of ***apoptosis*** , and the neighbouring cells rapidly incorporate the apoptotic cells, preventing the release of their content, hereby the induction of inflammation. Chemicals and irradiation can induce ***apoptosis*** , as well as crosslinkage of cell surface receptors. The best characterized receptors are the Fas receptor (Apo-1, CD95) and the TNFR1, having similar intracellular sequences, the 'death domain', which is necessary for the transduction of the apoptotic signal. There are intracellular adaptor molecules, associated with the death domain, which act as mediators between the receptors and the ICE-like (interleukin-1.beta. converting enzyme) proteases. ***Apoptosis*** have a central role in the maturation and functioning of the immune system. In mice mutations in the gene of the Fas receptor or its ligand result in impaired activation induced cell death, which leads to the development of an ***autoimmune*** lymphoproliferative syndrome, resembling systemic lupus erythematosus. Some alterations of ***apoptosis*** were also detected in patients with systemic ***autoimmune*** diseases as well as in some infectious deseases, such as AIDS and hepatitis. An important function of ***apoptosis*** is the elimination of malignant cells. However, genetic damage of some oncogens and tumour ***suppressor*** genes (e.g. p53) may lead to impairment regulation of ***apoptosis*** and results in the survival of the transformed cells.

L45 ANSWER 7 OF 31 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 1998:110456 SCISEARCH
THE GENUINE ARTICLE: YU399
TITLE: Mechanisms of systemic autoimmunity in murine models of SLE
AUTHOR: Eisenberg R (Reprint)
CORPORATE SOURCE: UNIV PENN, SCH MED, STELLAR CHANCE LABS 909, DIV
RHEUMATOL, DEPT MED, 422 CURIE DR, PHILADELPHIA, PA 19104 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: IMMUNOLOGIC RESEARCH, (1998) Vol. 17, No. 1-2, pp. 41-47.
Publisher: HUMANA PRESS INC, 999 RIVERVIEW DRIVE SUITE 208, TOTOWA, NJ 07512.
ISSN: 0257-277X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 31
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Our laboratory has utilized spontaneous and experimentally induced models of systemic autoimmunity in mice in order to elucidate the cellular deficiencies in immunoregulation that are essential to this process. In the spontaneously ***autoimmune*** mouse strains, genetic defects in T and B cell ***tolerance*** are the primary abnormalities that drive the syndrome. The induced chronic graft-vs-host model depends on abnormal T-B interactions resulting from allogeneic recognition of major histocompatibility complex (MHC) class II. Future investigations will target the biochemistry of the loss of ***tolerance*** and the specificity of autoreactive T cells that provide help for autoantibody production.

L45 ANSWER 8 OF 31 USPATFULL
ACCESSION NUMBER: 97:31611 USPATFULL

TITLE: Human anti-Fas IgG1 monoclonal antibodies
INVENTOR(S): Lynch, David H., Bainbridge Island, WA, United States
Alderson, Mark R., Bainbridge Island, WA, United States
PATENT ASSIGNEE(S): Immunex Corporation, Seattle, WA, United States (U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5620889	970415
APPLICATION INFO.:	US 94-322805	941013 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 93-159003, filed on 29 Nov 1993, now abandoned which is a continuation-in-part of Ser. No. US 93-136817, filed on 14 Oct 1993, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Loring, Susan A.
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 1698
AS INDEXING IS AVAILABLE FOR THIS PATENT.

The present invention provides a panel of monoclonal antibodies and binding proteins which specifically bind to human Fas antigen. Some of the antibodies and binding proteins are capable of stimulating T cell proliferation, inhibiting binding of anti-Fas CH-11 monoclonal antibody to cells expressing Fas antigen, blocking anti-Fas CH-11 monoclonal antibody-mediated lysis of cells, and blocking ***Fas*** ***ligand*** -mediated lysis of cells. The invention also provides for therapeutic compositions comprising the monoclonal antibodies.

L45 ANSWER 9 OF 31 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97404388 MEDLINE
DOCUMENT NUMBER: 97404388
TITLE: Precursor B cells for autoantibody production in genomically Fas-intact ***autoimmune*** disease are not subject to Fas-mediated immune elimination.
AUTHOR: Hirose S; Yan K; Abe M; Jiang Y; Hamano Y; Tsurui H; Shirai T
CORPORATE SOURCE: Department of Pathology, Juntendo University School of Medicine, Tokyo 113, Japan.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Aug 19) 94 (17) 9291-5.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199711
ENTRY WEEK: 19971103

AB The Fas/ ***Fas*** ***ligand*** (FasL) system participates in regulation of the immune system through the apoptotic process. However, the extent to which abnormalities in this system are involved in the loss of self- ***tolerance*** and development of ***autoimmune*** disease not associated with Fas/FasL mutations remains unknown. The present study addresses this issue in Fas/FasL-intact, systemic lupus erythematosus (SLE)-prone (NZB x NZW) (NZB/W) F1 mice. While splenic B cells from 2-month-old mice before overt SLE expressed Fas poorly, in vitro stimulation with an agonistic anti-CD40 mAb up-regulated their Fas expression, thus revealing the existence of two populations: one was Fashigh and highly susceptible to anti-Fas mAb-induced ***apoptosis*** , and the other was Faslow and ***apoptosis*** -resistant. The Faslow cells were included in the CD5(+) B cell subpopulation and contained most of the cells that produced IgM anti-DNA antibodies. The isotype of anti-DNA antibodies switches from IgM to IgG in NZB/W F1 mice at ages beginning at about 6 months. These IgG anti-DNA antibodies were produced almost exclusively by a subpopulation of splenic B cells that spontaneously expressed low levels of Fas in vivo and were ***apoptosis*** -resistant. The findings indicate that precursor B cells for autoantibody production and presumably autoantibody-secreting cells in these mice are relatively resistant to Fas-mediated ***apoptosis*** , a finding supporting the concept that abnormalities of Fas-mediated apoptotic process are involved in the development of autoreactive B cells in Fas/FasL-intact ***autoimmune*** disease.

L45 ANSWER 10 OF 31 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 97:299496 SCISEARCH
THE GENUINE ARTICLE: WT196
TITLE: Functional responses and ***apoptosis*** of CD25 (IL-2R alpha)-deficient T cells expressing a transgenic antigen receptor
AUTHOR: VanParijs L; Biuckians A; Ibragimov A; Alt F W; Willerford D M; Abbas A K (Reprint)
CORPORATE SOURCE: LMRC-521, 221 LONGWOOD AVE, BOSTON, MA 02115 (Reprint); BRIGHAM & WOMENS HOSP, DEPT PATHOL, DIV IMMUNOL RES, BOSTON, MA 02115; HARVARD UNIV, SCH MED, BOSTON, MA 02115; CHILDRENS HOSP, MED CTR, HOWARD HUGHES MED INST, BOSTON, MA 02115; CHILDRENS HOSP, MED CTR, DEPT GENET, BOSTON, MA 02115; CHILDRENS HOSP, MED CTR, DEPT PEDIAT, BOSTON, MA 02115
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF IMMUNOLOGY, (15 APR 1997) Vol. 158, No. 8, pp. 3738-3745.
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0022-1767.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 27

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB IL-2 was initially defined as a T lymphocyte growth factor, but recent studies have provided evidence that it may also play a role in regulating T cell differentiation, ***apoptosis*** , and ***tolerance*** . To examine the contribution of IL-2 to these processes, we have bred a class II-restricted TCR transgene into mice deficient in the alpha-chain of the IL-2R, CD25. We show that in response to Ag, T cells from these mice are unable to use IL-2 and, as a result, are less efficient at traversing the cell cycle, and proliferate less than wild-type cells. Furthermore, CD25 -/- T cells exhibit reduced survival in vitro, even in the presence of costimulatory signals. IL-4 and IL-15, a cytokine related to IL-2, enhance the survival and Ag-induced proliferation of CD25 -/- T cells. Activated CD25 -/- T cells are resistant to Fas-mediated activation-induced cell death (AICD), and this defect cannot be corrected by other cytokines. Therefore, IL-2 plays a unique role in regulating AICD, but has redundant roles in T cell survival and proliferation in vitro. The failure of AICD observed with CD25 -/- T cells may explain the unexpected observation that deficiency of IL-2 or of the alpha- or beta-chain of the IL-2R results not in immunodeficiency, but in ***autoimmune*** disease.

L45 ANSWER 11 OF 31 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97474763 MEDLINE
DOCUMENT NUMBER: 97474763
TITLE: Amelioration of collagen-induced arthritis by CD95 (Apo-1/ ***Fas***)- ***ligand*** gene transfer.
AUTHOR: Zhang H; Yang Y; Horton J L; Samoilova E B; Judge T A; Turka L A; Wilson J M; Chen Y
CORPORATE SOURCE: Institute for Human Gene Therapy, Department of Molecular and Cellular Engineering, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1997 Oct 15) 100 (8) 1951-7.
Journal code: HS7. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104

AB Both rheumatoid arthritis and animal models of ***autoimmune*** arthritis are characterized by hyperactivation of synovial cells and hyperplasia of the synovial membrane. The activated synovial cells produce inflammatory cytokines and degradative enzymes that lead to destruction of cartilage and bones. Effective treatment of arthritis may require elimination of most or all activated synovial cells. The death factor Fas/Apo-1 and its ligand (FasL) play pivotal roles in maintaining self- ***tolerance*** and immune privilege. Fas is expressed constitutively in most tissues, and is dramatically upregulated at the site of inflammation. In both rheumatoid arthritis and animal models of ***autoimmune*** arthritis, high levels of Fas are expressed on activated synovial cells and infiltrating leukocytes in the inflamed joints. Unlike Fas, however, the levels of FasL expressed in the arthritic joints are extremely low, and most activated synovial cells survive despite high levels of Fas expression. To upregulate FasL expression in the arthritic joints, we have generated a recombinant replication-defective adenovirus carrying FasL gene; injection of the FasL virus into inflamed joints conferred high levels of FasL expression, induced ***apoptosis*** of synovial cells, and ameliorated collagen-induced arthritis in DBA/1 mice. The ***Fas*** - ***ligand*** virus also inhibited production of interferon-gamma by collagen-specific T cells. Coadministration of Fas-immunoglobulin fusion protein with the ***Fas*** - ***ligand*** virus prevented these effects, demonstrating the specificity of the ***Fas*** - ***ligand*** virus. Thus, FasL gene transfer at the site of inflammation effectively ameliorates ***autoimmune*** disease.

L45 ANSWER 12 OF 31 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 97180739 MEDLINE
DOCUMENT NUMBER: 97180739
TITLE: Clincial, immunologic, and genetic features of an ***autoimmune*** lymphoproliferative syndrome associated with abnormal lymphocyte ***apoptosis***
AUTHOR: Sneller M C; Wang J; Dale J K; Strober W; Middelton L A; Choi Y; Fleisher T A; Lim M S; Jaffe E S; Puck J M; Lenardo M J; Straus S E
CORPORATE SOURCE: Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.
SOURCE: BLOOD, (1997 Feb 15) 89 (4) 1341-8.
Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199705
ENTRY WEEK: 19970504

AB Programmed cell death (***apoptosis***) of activated lymphocytes is critical to immune homeostasis. The cell surface protein Fas (CD95) and its ligand play a pivotal role in regulating lymphocyte ***apoptosis*** , and defective expression of either Fas or ***Fas*** ***ligand*** results in marked over accumulation of mature lymphocytes and ***autoimmune*** disease in mice. The results of recent studies suggest that defective lymphocyte ***apoptosis*** caused by mutations of the Fas gene can result in a severe ***autoimmune*** lymphoproliferative syndrome (ALPS) in humans. To define the clinical, genetic, and immunologic spectrum of ALPS, 9 patients and their families were extensively evaluated with routine clinical studies, lymphocyte phenotyping, genotyping, and in vitro assays for lymphocyte ***apoptosis*** . Individual patients were followed up for 3 months to 6 years. ALPS was identified in 9 unrelated children as manifested by moderate to massive splenomegaly and lymphadenopathy, hypergammaglobulinemia, autoimmunity, B-cell lymphocytosis, and the expansion of an unusual population of CD4- CD8- T cells that express the alpha/beta T-cell receptor (TCR). All patients showed defective lymphocyte ***apoptosis*** in vitro. Heterozygous mutations of the Fas gene were detected in 8 patients. One ALPS patient lacked a Fas gene mutation. Healthy relatives with Fas mutations were identified in 7 of 8 ALPS kindreds. These relatives also showed in vitro abnormalities of Fas-mediated lymphocyte ***apoptosis*** , but clinical features of ALPS were

not present in the vast majority of these individuals. ALPS is a unique clinical syndrome in which in vitro abnormalities of lymphocyte ***apoptosis*** are associated with abnormal lymphoproliferation and autoimmunity. These findings provide evidence that ***apoptosis*** of activated lymphocytes is an important mechanism for maintaining immunologic homeostasis and self- ***tolerance*** in humans. Fas gene mutations account for impaired lymphocyte ***apoptosis*** in only a subset of patients with ALPS.

L45 ANSWER 13 OF 31 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998098797 MEDLINE
DOCUMENT NUMBER: 98098797
TITLE: Cell biology in endogenous uveitis.
AUTHOR: Nakamura S; Sugita M; Igai O; Toriyama S; Ono S
CORPORATE SOURCE: Department of Ophthalmology, Yokohama City University School of Medicine.
SOURCE: NIPPON GANKA GAKKAI ZASSHI. ACTA SOCIETATIS OPHTHALMOLOGICAE JAPONICAE, (1997 Dec) 101 (12) 975-86.
Journal code: 22O. ISSN: 0029-0203.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
ENTRY MONTH: 199805
ENTRY WEEK: 19980503
AB We studied the immune system in 18 cases of Behcet's disease with ocular involvement. The proportion of CD69+ cells in CD4+ cells was significantly higher in patients with active uveoretinitis than in normal controls ($p < 0.01$). After OKT-3 stimulation of cultured cells, the proportion was significantly increased in controls ($p < 0.01$) but not in patients. ***Fas*** - ***ligand*** positive cells in CD8+ cells in patients did not increase after OKT-3 stimulation. Thus, the T cells in patients were in an activated state in vivo but were not further activated by OKT-3 stimulation. Cultured lymphocytes of patients after OPT-3 activation and anti-Fas antibody stimulation showed that the T cells in the active stage of the disease were resistant to ***apoptosis*** and unlikely to undergo regression by activation-induced cell death (AICD). The mean level of soluble Fas antigen was significantly elevated in sera of patients with active uveoretinitis as compared with normal controls ($p < 0.05$). TdT-mediated dUTP-biotin nick end labelling (TUNEL)-positive infiltrating cells were present in the inflamed retina and the posterior chamber in experimental ***autoimmune*** uveoretinitis (EAU) in rats, suggesting the involvement of ***apoptosis*** of infiltrated cells in the regression of inflammation. Serum concentration of tumor necrosis factor-alpha (TNF-alpha) was significantly elevated after 9 days of immunization in rats ($p < 0.02$). The inflammation score was ***suppressed*** by intravenous administration of anti-TNF-alpha antibody from days 7 to 14. It is concluded that intraocular inflammation in Behcet's disease is associated with activation of T cells and abnormality in ***apoptosis*** and AICD mechanisms. Systemic anti-TNF-alpha antibody promises to be of value in the treatment of the disease.

L45 ANSWER 14 OF 31 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 1998:137271 SCISEARCH
THE GENUINE ARTICLE: YW017
TITLE: Molecules involved in cell death and peripheral ***tolerance***
AUTHOR: Wang J (Reprint); Lenardo M J
CORPORATE SOURCE: NIAID, IMMUNOL LAB, NIH, BLDG 10, ROOM 11D09, 10 CTR
DR, MSC 1892, BETHESDA, MD 20892 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: CURRENT OPINION IN IMMUNOLOGY, (DEC 1997) Vol. 9, No. 6, pp. 818-825.
Publisher: CURRENT BIOLOGY LTD, 34-42 CLEVELAND STREET, LONDON, ENGLAND W1P 6LB.
ISSN: 0952-7915.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 91
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB ***Apoptosis*** is important far maintaining peripheral lymphocyte homeostasis and for minimizing the accumulation of autoreactive lymphocytes. Disruption of apoptotic pathways has been linked to lymphadenopathy, breakdown of peripheral ***tolerance*** and the development of ***autoimmune*** diseases. Major progress has been made during the past year in understanding the critical roles of a variety of signaling molecules, especially a group of cysteine proteases, for the execution of ***apoptosis*** . These proteases appear to be the primary effector molecules responsible for carrying out lymphocyte ***apoptosis*** and may be critical for peripheral immunological ***tolerance*** .

L45 ANSWER 15 OF 31 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97165076 MEDLINE
DOCUMENT NUMBER: 97165076
TITLE: Peripheral deletion of rheumatoid factor B cells after abortive activation by IgG.
AUTHOR: Tighe H; Warnatz K; Brinson D; Corr M; Weigle W O; Baird S M; Carson D A
CORPORATE SOURCE: Department of Medicine, University of California at San Diego, La Jolla 92093-0663, USA.
CONTRACT NUMBER: AR42153 (NIAMS)
AR25443 (NIAMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF
THE UNITED STATES OF AMERICA, (1997 Jan 21) 94 (2) 646-51.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199705
ENTRY WEEK: 19970502
AB Rheumatoid factor (RF) B cells proliferate during secondary immune responses to immune complexed antigen and antigen specific T cells, but higher affinity RFs are not detected except in patients with rheumatoid arthritis and other ***autoimmune*** diseases. Consequently, there must exist highly efficient mechanisms for inactivation of these higher-affinity RF B cell clones under normal circumstances. Exposure of transgenic mice expressing a human IgM RF to soluble human IgG in the absence of T cell help causes antigen specific B cell deletion in 2-3 days. The deletion is independent of the Fas/ ***Fas*** ***ligand*** (FasL) pathway of ***apoptosis*** and is preceded by a phase of partial activation involving increase in cell size and expression of B7 and ICAM-1, and transient release of low levels of immunoglobulin. Complete B cell activation involving the formation of germinal centers and sustained high level RF secretion only occurs if T cell help is provided simultaneously. RF B cells exposed to tolerogen remain competent to secrete RF in vitro if provided with an appropriate antigenic stimulus and T cell help. Consequently, death of these cells is not preceded by anergy. Abortive activation/deletion of B cells by antigen in the absence of T cell-derived survival signals may represent the major mechanism for maintaining peripheral ***tolerance*** in B cells expressing higher affinity RF. The lack of anergy, and the potential for reactivation before death, provide a means for maintaining RF production under pathologic circumstances, such as may occur in the inflamed rheumatoid synovium.

L45 ANSWER 16 OF 31 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97411274 MEDLINE
DOCUMENT NUMBER: 97411274
TITLE: Studies on ***Fas*** ***ligand*** expression in patients with systemic lupus erythematosus.
AUTHOR: Feng Y
CORPORATE SOURCE: Second Department of Internal Medicine, Hokkaido University School of Medicine, Sapporo, Japan.
SOURCE: HOKKAIDO IGAKU ZASSHI. HOKKAIDO JOURNAL OF MEDICAL
SCIENCE, (1997 Jul) 72 (4) 443-55.
Journal code: GA9. ISSN: 0367-6102.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104
AB The Fas/ ***Fas*** ***ligand*** (FasL)-mediated ***apoptosis*** may play a role in the induction and maintenance of T cell ***tolerance*** . To investigate the role of FasL in the ***apoptosis*** of lymphocytes in ***autoimmune*** diseases, gene and protein expression of FasL were examined in peripheral blood mononuclear cells (PBMC) from patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), and from healthy donors by a newly-designed semiquantitative reverse transcription (RT)-PCR and flow cytometry. Although no significant difference in FasL gene expression was obtained among three groups, SLE patients exhibited a wide distribution of the values. In SLE patients, there was a significant correlation between FasL gene expression by PBMC and some clinical parameters including SLE Disease Activity Index (SLEDAI) score, anti-DNA antibody titer and complement titer (CH50). More interestingly, a marked increase in FasL gene expression was observed in untreated SLE patients, whereas a significant decrease was observed in prednisolone-treated SLE patients. Flow cytometric analysis revealed the expression of FasL on T cell subsets from SLE patients and on anti-CD3 mAb-stimulated T cells from healthy donors. In vitro experiments, dexamethasone inhibited FasL gene expression by PBMC from healthy donors in a dose-dependent manner and with time of incubation. These results clearly indicate that FasL is up-regulated in active SLE patients, reflecting in vivo T cell activation, and that corticosteroids directly down-regulate FasL gene expression by human PBMC.

L45 ANSWER 17 OF 31 BIOSIS COPYRIGHT 1998 BIOSIS DUPLICATE 7
ACCESSION NUMBER: 97:488225 BIOSIS
DOCUMENT NUMBER: 99787428
TITLE: ***Apoptosis*** with FasL+ cell infiltration in the periphery and thymus of corrected ***autoimmune*** mice.
AUTHOR(S): Kobata T; Takasaki K; Asahara H; Hong N M; Masuko-Hongo K; Kato T; Hirose S; Shirai T; Kayagaki N; Yagita H; Okumura K; Nishioka K
CORPORATE SOURCE: Rheumatol. Immunol. Genetics Programs, Inst. Med. Sci., St. Marianna Univ. Sch. Med., 2-16-1 Sugao, Miyamae-ku, Kawasaki 216, Japan
SOURCE: Immunology 92 (2). 1997. 206-213. ISSN: 0019-2805
LANGUAGE: English
AB Fas (CD95) ligand (L) is a death factor that binds to its receptor, Fas, and induces apoptotic cell death, a crucial process in immunological ***tolerance*** . gld (generalized lymphoproliferative disorder) mice, which have a point mutation in the FasL gene, develop spontaneous systemic ***autoimmune*** syndromes characterized by hypergammaglobulinaemia and lymphoid hyperplasia owing to accumulation of abnormal B220+ CD3+ cells. Transplantation of wild-type (wt) bone marrow cells into old gld mice on the same strain background results in normalization of ***autoimmune*** syndromes. We characterized the cellular mechanisms (functionally and histologically) of the above phenomena in gld mice after bone marrow transplantation (BMT) to determine the role of ***apoptosis*** via Fas/FasL interactions in inducing and maintaining self- ***tolerance*** in vivo. Activated splenocytes from wt and BMT (wt to gld) mice showed significant cytotoxic activity against Fas-transfectant cells while those from BMT (gld to gld) mice did not. Cells in the thymus, spleen and lymph nodes of gld mice uniformly upregulated Fas expression and were sensitive to Fas-mediated ***apoptosis*** compared with those in wt mice. Cells sensitive to Fas-mediated ***apoptosis*** in gld mice resided not only among abnormal B220+ CD3+ cells but also among conventional lymphocytes. More importantly, histological analysis revealed that cells in the spleen, lymph nodes and thymus frequently underwent ***apoptosis*** with infiltration of FasL+ cells in BMT (wt to gld) mice compared with BMT (gld to gld) mice. Our results indicated that ***apoptosis*** via Fas/FasL interactions can directly eliminate pathogenic cells responsible for autoimmunity in the periphery and possibly in the thymus in vivo.

L45 ANSWER 18 OF 31 BIOSIS COPYRIGHT 1998 BIOSIS
ACCESSION NUMBER: 98:157778 BIOSIS

DOCUMENT NUMBER: 01157778
TITLE: Transfusion of ***Fas*** ***ligand*** expressing APCs as a therapy for ***autoimmune*** disease.
AUTHOR(S): Zhang H-G; Sun D; Curiel D T; Mountz J D; Zhou T
CORPORATE SOURCE: Univ. Ala. at Birmingham, Birmingham, AL 35294, USA
SOURCE: 61st National Scientific Meeting of the American College of Rheumatology and the 32nd National Scientific Meeting of the Association of Rheumatology Health Professionals, Washington, DC, USA, November 8-12, 1997. Arthritis & Rheumatism 40 (9 SUPPL.). 1997. S172. ISSN: 0004-3591
DOCUMENT TYPE: Conference
LANGUAGE: English

L45 ANSWER 19 OF 31 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998101503 MEDLINE
DOCUMENT NUMBER: 98101503
TITLE: Why do defects in the Fas- ***Fas*** ***ligand*** system cause autoimmunity?
AUTHOR: Suda T; Nagata S
CORPORATE SOURCE: Department of Molecular Biology, Osaka Bioscience Institute, Japan.
SOURCE: JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1997 Dec) 100 (6 Pt 2) S97-101. Ref: 46
Journal code: H53. ISSN: 0091-6749.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199804
ENTRY WEEK: 19980401
AB We have previously isolated genes that encode Fas and ***Fas*** ***ligand*** , a receptor-ligand pair that mediates an apoptotic signal. We also have demonstrated that lpr and gld mice, well-known animal models of ***autoimmune*** disease are loss-of-function mutants of the Fas and ***Fas*** ***ligand*** genes, respectively. Patients with ***autoimmune*** lymphoproliferative disorders have been found to bear mutations of the Fas gene. These findings indicate that the Fas- ***Fas*** ***ligand*** system plays an important role in the maintenance of self- ***tolerance*** among both humans and mice. During T-cell development, mouse T cells initially express Fas in the thymus and maintain their expression thereafter. Peripheral B cells usually express Fas at much lower levels than do T cells, but various stimuli enhance Fas expression on B cells. In contrast, among the lymphocyte subsets, only activated T cells and natural killer cells express readily detectable levels of ***Fas*** ***ligand*** . Reactivation of previously activated T cells through T-cell receptors induces ***apoptosis*** . This phenomenon (activation-induced cell death) is mediated by means of the Fas- ***Fas*** ***ligand*** interaction. We recently discovered that peripheral naive T cells in mice are susceptible to ***Fas*** ***ligand*** but not to agonistic anti-Fas antibodies. To our surprise, engagement of T-cell receptors on naive T cells was shown to induce ***Fas*** ***ligand*** resistance. On the basis of these findings and other reports, we discuss how the breakdown of self- ***tolerance*** occurs as the result of defects in the Fas- ***Fas*** ***ligand*** system.

L45 ANSWER 20 OF 31 BIOSIS COPYRIGHT 1998 BIOSIS
ACCESSION NUMBER: 97:345836 BIOSIS
DOCUMENT NUMBER: 99645039
TITLE: Antigen-induced death of T-lymphocytes.
AUTHOR(S): Kabelitz D; Janssen O
CORPORATE SOURCE: Dep. Immunol., Paul-Ehrlich-Inst., P.O. Box, D-63207 Langen, Germany. Available: http://www.bioscience.org./1997/v2/d/kabelit1/html s/61-77.htm
SOURCE: Frontiers in Bioscience (online) 2 (CITED JULY 1, 1997). 1997. D61-77.
LANGUAGE: English
AB Resting mature T-lymphocytes are activated when they are triggered via their antigen-specific T-cell receptor (TCR) molecule or the associated CD3 antigen. In contrast, preactivated T-cells can undergo activation-induced cell death (AICD) in response to the same signals. Stimulation of activated T-cells upregulates the expression of the ***Fas*** - ***ligand*** , and the interaction of ***Fas*** - ***ligand*** with the corresponding Fas receptor triggers an ***apoptosis*** program that culminates in cellular suicide usually associated with the fragmentation of DNA into oligonucleosomal bands. Molecular evidence indicates that proteases related to interleukin-1-beta converting enzyme play an essential role in the execution of cell death. AICD of mature T-lymphocytes can be efficiently triggered by monoclonal antibodies against the CD3/TCR complex, or by superantigens such as bacterial enterotoxins. Although it is more difficult to induce AICD by conventional peptide antigens, it is now clear that antigen-induced AICD is a powerful means of eliminating antigen-reactive T-cells. Therefore, AICD contributes to the regulation (i.e., termination) of cellular immune responses. In addition, AICD might play a role in the establishment of peripheral immune ***tolerance*** . Increased knowledge of the molecular mechanisms of AICD opens new immunotherapeutical perspectives for the treatment of certain ***autoimmune*** diseases, and will have implications in other areas such as transplantation medicine.

L45 ANSWER 21 OF 31 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 96:866011 SCISEARCH
THE GENUINE ARTICLE: VT588
TITLE: Nutrition and ***apoptosis***
AUTHOR: Troyer D; Fernandes G (Reprint)
CORPORATE SOURCE: 7703 FLOYD CURL DR, SAN ANTONIO, TX 78284 (Reprint);
UNIV TEXAS, CTR HLTH SCI, DEPT PATHOL, SAN ANTONIO, TX 78284; UNIV TEXAS, CTR HLTH SCI, DEPT MED, SAN ANTONIO, TX 78284
COUNTRY OF AUTHOR: USA
SOURCE: NUTRITION RESEARCH, (NOV-DEC 1996) Vol. 16, No. 11-12, pp. 1959-1987.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB.
ISSN: 0271-5317.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 176
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The objective of this review is to summarize information about the role of ***apoptosis*** in mediating the effects of nutritional interventions which prolong life span, ***suppress*** ***autoimmune*** diseases, and decrease tumorigenesis. Nutritional interventions such as calorie restriction (CR) likely postpone the accumulation of damaging effects that accompany ad libitum (AL) food intake and aging. However, the beneficial effects of CR or other nutritional interventions may not be limited to progressive, slowly accumulating events, but may also include important effects during growth and development. An example of the latter would include modulation of the selection and editing processes occurring in the thymus during maturation of the immune system. Regulation of ***apoptosis*** may be particularly relevant to these developmental processes, though decreased ***apoptosis*** also plays a role in the pathogenesis of ***autoimmune*** diseases and age-related events such as tumorigenesis. Therefore, we will review the evidence that increased ***apoptosis*** mediates the effect of CR (and/or supplementation with omega-3 fatty acids), ***suppresses*** tumors, ameliorates ***autoimmune*** diseases, and prolongs life span. Copyright (C) 1996 Elsevier Science Inc.

L45 ANSWER 22 OF 31 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 96:330061 SCISEARCH
THE GENUINE ARTICLE: UH144
TITLE: INHIBITION OF NUR77/NURR1 LEADS TO INEFFICIENT CLONAL DELETION OF SELF-REACTIVE T-CELLS
AUTHOR: ZHOU T (Reprint); CHENG J H; YANG P; WANG Z; LIU C D; SU X; BLUETHMANN H; MOUNTZ J D
CORPORATE SOURCE: UNIV ALABAMA, DEPT MED, DIV CLIN IMMUNOL & RHEUMATOL, 701 S 19TH ST, LHRB 473, BIRMINGHAM, AL, 35294 (Reprint); VET ADM MED CTR, BIRMINGHAM, AL, 35233; F HOFFMANN LA ROCHE & CO LTD, PHARMACEUT RES GENE TECHNOL, CH-4002 BASEL, SWITZERLAND
COUNTRY OF AUTHOR: USA; SWITZERLAND
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (01 APR 1996) Vol. 183, No. 4, pp. 1879-1892.
ISSN: 0022-1007.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 75
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The Nu77/Nurr1 family of DNA binding proteins has been reported to be required for the signal transduction of CD3/T cell receptor (TCR)-mediated ***apoptosis*** in T cell hybridomas. To determine the role of this family of DNA-binding proteins in thymic clonal deletion, transgenic (Tg) mice bearing a dominant negative mutation were produced. The transgene consisted of a truncated Nur77 (Delta Nur77) gene encoding tile DNA-binding domain of Nur77 ligated to a TCR-beta enhancer resulting in early expression in thymocytes. ***Apoptosis*** of CD4(+)CD8(+) thymocytes mediated by CD3/TCR signaling was greatly inhibited in the Delta Nur77 Tg mice, compared with non-Tg littermates, after treatment with anti-CD3 or anti-TCR antibody in vivo and in vitro, Clonal deletion of self-reactive T cells was investigated in Delta Nur77-D-b/HY TCR-alpha/beta double Tg mice. There was a five-fold increase in the total number of thymocytes expressing self-reactive D-b/HY TCR-alpha/beta in the Delta Nur77-TCR-alpha/beta double Tg male mice. Deficient clonal deletion of self-reactive thymocytes was demonstrated by a 10-fold increase in the CD4(+)CD8(+) thymocytes that expressed Tg TCR-alpha/beta There was an eight-fold increase in CD8(+), D-b/HY TCR-alpha/beta T cells in tile lymph nodes (LN) of Delta Nur77-D-b/HY TCR-alpha/beta double Tg compared with D-b/HY TCR-alpha/beta Tg male mice. In spite of defective clonal deletion, the T cells expressing the Tg TCR were functionally anergic. In vivo analysis revealed increased activation and ***apoptosis*** of T cells associated with increased expression of Fas and ***Fas*** ***ligand*** in LN of Delta Nur77-D-b/HY TCR-alpha/beta double Tg male mice. These results indicate that inhibition of Nur77/Nurr1 DNA binding in T cells leads to inefficient thymic clonal deletion, but T cell ***tolerance*** is maintained by Fas-dependent clonal deletion in LN and spleen.

L45 ANSWER 23 OF 31 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 96:422102 SCISEARCH
THE GENUINE ARTICLE: UN188
TITLE: FAS (CD95)-INDEPENDENT REGULATION OF IMMUNE-RESPONSES BY ANTIGEN-SPECIFIC CD4(-)CD8(+) T-CELLS
AUTHOR: TEH S J; DUTZ J P; MOTYKA B; TEH H S (Reprint)
CORPORATE SOURCE: UNIV BRITISH COLUMBIA, DEPT MICROBIOL & IMMUNOL,
VANCOUVER, BC V6T 1Z3, CANADA (Reprint); UNIV BRITISH COLUMBIA, DEPT MICROBIOL & IMMUNOL, VANCOUVER, BC V6T 1Z3, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: INTERNATIONAL IMMUNOLOGY, (MAY 1996) Vol. 8, No. 5, pp. 675-681.
ISSN: 0953-8178.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 31
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Antigen-activated T cells of the CD4(+)CD8(-) and the CD4(-)CD8(+) phenotype are susceptible to antigen receptor-stimulated cell death, This form of apoptotic cell death has been shown to be dependent on the expression of the Fas (CD95) antigen and can occur via an autocrine mechanism involving the concomitant up-regulation of Fas and its ligand on activated T cells. Mutations in genes encoding Fas (lpr) and the ***Fas*** ***ligand*** (gld) contribute to the development of an ***autoimmune*** syndrome similar to systemic lupus erythematosus

in mice. These observations led to the suggestion that the Fas signaling pathway is an important regulator of immune responses in vivo. Here we evaluated the importance of the Fas pathway in regulating immune responses by male antigen-specific CD4(-)CD8(+) T cells, We found that the in vivo elimination of male antigen-activated cells was independent of Fas expression by these cells, However, the elimination of these activated cells was inhibited by the transgenic expression of Bcl-2, a protein that inhibits multiple forms of apoptotic cell death, The transgenic Bcl-2 protein also inhibited the death of male antigen-activated cells following IL-2 deprivation. Cell death resulting from IL-2 deprivation occurred efficiently in male antigen-activated Fas(-) cells, We propose that the rapid deletion of male antigen-activated Fas(-) cells in vivo is due to limiting amounts of IL-2 that are available in the microenvironment of the activated cells at the peak of the response.

L45 ANSWER 24 OF 31 MEDLINE
ACCESSION NUMBER: 97089023 MEDLINE
DOCUMENT NUMBER: 97089023
TITLE: Cellular interactions in the lpr and gld models of systemic autoimmunity.
AUTHOR: Sobel E S
CORPORATE SOURCE: Department of Medicine, University of Florida, Gainesville 32610, USA.
SOURCE: ADVANCES IN DENTAL RESEARCH, (1996 Apr) 10 (1) 76-80.
Ref: 59
Journal code: ADD. ISSN: 0895-9374.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Dental Journals; Dental
ENTRY MONTH: 199702
ENTRY WEEK: 19970204
AB The lpr and gld murine models have been important contributors to our understanding of systemic ***autoimmune*** diseases. Mice homozygous for either of these autosomal recessive genes develop a phenotypically identical disease characterized by the accumulation of CD4-CD8- T-cells and the production of a wide spectrum of autoantibodies. The lpr (lymphoproliferation) mutation encodes a defective Fas ***apoptosis*** receptor gene. More recently, gld (generalized lymphadenopathy) has been shown to be a point mutation in the ***Fas*** ***ligand*** gene. Despite the molecular characterization of these mutations, the exact mechanism by which ***tolerance*** is lost is still unknown, although in vivo cell transfer studies have provided clues. Chimera studies, in which normal and lpr bone marrow were co-infused into lpr mice, demonstrated not only that the normal Fas receptor is functionally expressed in both T- and B-cells, but that the Fas mutation is required in both for full expression of the lpr phenotype. Conversely, in analogous experiments with gld mice, co-infusion of normal and gld bone marrow largely prevented the development of autoantibodies. Sporadic autoantibody titers were seen in some mice, but were derived from both donors. The effects on T-cells were subtly different: The CD4-CD8- T-cells were also greatly reduced in number, but all were of gld origin. These data indicate that the gld defect is extrinsic to B-cells but only partially extrinsic to T-cells, and suggest that ***Fas*** ***ligand*** in T-cells may have an autocrine and paracrine function.

L45 ANSWER 25 OF 31 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 96:168388 SCISEARCH
THE GENUINE ARTICLE: TW581
TITLE: ***SUPPRESSION*** AND REVERSAL OF GLD DISEASE BY PARABIOSIS WITH NORMAL MICE
AUTHOR: KAKKANAIAH V N; MACDONALD G C; COHEN P L; EISENBERG R A (Reprint)
CORPORATE SOURCE: UNIV PENN, DIV RHEUMATOL, 422 CURIE BLVD, PHILADELPHIA, PA, 19104 (Reprint); UNIV N CAROLINA, DEPT MED, CHAPEL HILL, NC, 27599; UNIV N CAROLINA, DEPT MICROBIOL IMMUNOL, CHAPEL HILL, NC, 27599
COUNTRY OF AUTHOR: USA
SOURCE: CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY, (JAN 1996)
Vol. 78, No. 1, pp. 6-13.
ISSN: 0090-1229.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: ENGLISH
REFERENCE COUNT: 31
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The disruption of the Fas receptor or ***Fas*** ***ligand*** by the lpr or gld mutations, respectively, results in severe ***autoimmune*** and lymphoproliferative disease due to the failure of Fas-mediated deletion of self-reactive lymphocytes, Recently, we have shown in mixed chimeras that gld-induced autoimmunity could be corrected by normal bone marrow, in particular by normal T cells, In contrast, lpr-mediated autoimmunity could not be influenced by normal bone marrow-derived cells. In the present report, we have studied the role of normal lymphocytes in ***suppressing*** or reversing gld-induced autoimmunity by parabiosis with normal mice. Our results show a ***suppression*** of lymphadenopathy, fewer CD4(-)CD8(-) T cells, and lower levels of autoantibody production in gld mice parabiosed with normal mice at 4-6 weeks of age. The gld mice parabiosed with normal mice at 4 months of age also exhibited a substantial reduction of both total and CD4(-)CD8(-) T cells in the periphery 2 months after surgery. However, they showed little reduction of autoantibodies compared to gld mice parabiosed with gld mice. In contrast, older lpr mice did not exhibit any reduction in lymphadenopathy or autoantibody production after parabiosis with normal mice. The prevention or reversal of lymphadenopathy in parabiosed gld mice suggests that ongoing Fas-mediated deletion in the periphery may play an important role in maintaining self- ***tolerance*** . The relative irreversibility of autoantibody synthesis in older parabiosed gld mice suggests that autoantibody-producing B cells or their committed precursors are long lived and do not express functional Fas receptor. (C) 1996 Academic Press Inc.

L45 ANSWER 26 OF 31 WPIDS COPYRIGHT 1998 DERWENT INFORMATION LTD
ACCESSION NUMBER: 95-169968 [22] WPIDS
CROSS REFERENCE: 97-235187 [21]
DOC. NO. CPI: C95-078983
TITLE: Monoclonal antibodies which specifically bind to human Fas antigen - capable of stimulating T cell proliferation or blocking anti-Fas CH-11. MAb-mediated lysis of cells..
DERWENT CLASS: B04 D16
INVENTOR(S): ALDERSON, M; LYNCH, D H
PATENT ASSIGNEE(S): (IMMV) IMMUNEX CORP
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9510540	A1	950420 (9522)*		EN	42
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP KR NZ					
AU 9479784	A	950504 (9536)			
EP 723556	A1	960731 (9635)		EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
JP 09503672	W	970415 (9725)			63
NZ 275711	A	980325 (9818)			

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9510540	A1	WO 94-US11632	941013
AU 9479784	A	AU 94-79784	941013
EP 723556	A1	EP 94-930757	941013
		WO 94-US11632	941013
JP 09503672	W	WO 94-US11632	941013
		JP 95-512047	941013
NZ 275711	A	NZ 94-275711	941013
		WO 94-US11632	941013

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9479784	A Based on	WO 9510540
EP 723556	A1 Based on	WO 9510540
JP 09503672	W Based on	WO 9510540
NZ 275711	A Based on	WO 9510540

PRIORITY APPLN. INFO: US 93-159003 931129; US 93-136817 931014
AB WO 9510540 A UPAB: 970530
An IgG1 monoclonal antibody (I) that specifically binds to the extracellular domain of human Fas antigen and at a 10-fold molar excess inhibits binding of anti-Fas CH-11 monoclonal antibody (MAb) to cells expressing Fas antigen within a range from 4-62%, is claimed.
USE - The MAbs block binding of CH-11 to cells expressing Fas antigen or block CH-11 mediated or Fas-L-mediated lysis of lymphoid cell lines, and are useful in research applications to provide insight into its role in normal immune responses as well as in the generation of ***autoimmune*** diseases. The blocking antibodies are also useful in therapeutic applications requiring inhibition of Fas- or Fas L-mediated biological activity. The compsn. is used in ***suppressing*** ***Fas*** ***ligand*** -mediated ***apoptosis*** .

L45 ANSWER 27 OF 31 SCISEARCH COPYRIGHT 1998 ISI (R)
ACCESSION NUMBER: 95:285525 SCISEARCH
THE GENUINE ARTICLE: QU825
TITLE: ***FAS*** ***LIGAND*** -MEDIATED CYTOTOXICITY IS DIRECTLY RESPONSIBLE FOR ***APOPTOSIS*** OF NORMAL CD4(+) T-CELLS RESPONDING TO A BACTERIAL SUPERANTIGEN
AUTHOR: ETTINGER R; PANKA D J; WANG J K M; STANGER B Z; JU S T; MARSHAKROTHSTEIN A (Reprint)
CORPORATE SOURCE: BOSTON UNIV, SCH MED, DEPT MICROBIOL, BOSTON, MA, 02118 (Reprint); BOSTON UNIV, SCH MED, DEPT MICROBIOL, BOSTON, MA, 02118; BOSTON UNIV, SCH MED, DEPT PATHOL & LAB MED, BOSTON, MA, 02118; BOSTON UNIV, SCH MED, CTR ARTHRITIS, BOSTON, MA, 02118; HARVARD UNIV, SCH MED, DEPT GENET, BOSTON, MA, 02115
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF IMMUNOLOGY, (01 MAY 1995) Vol. 154, No. 9, pp. 4302-4308.
ISSN: 0022-1767.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 27
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Exposure of naive CD4(+) T lymphocytes to superantigens such as staphylococcal enterotoxin B (SEE) induces a strong proliferative response. Prolonged exposure or subsequent restimulation of the responding T cell population with SEE leads to the apoptotic events of activation-induced cell death (AICD). However, T cells derived from either Fas-deficient lpr or ***Fas*** ***ligand*** -deficient gld ***autoimmune*** mouse strains, fail to undergo AICD under these conditions. Instead, these ***autoimmune*** T cells mount a vigorous proliferative response, suggesting a critical role for Fas/FasL interactions in this form of autoapoptosis. In the current study, we found that SEE-induced AICD was tied to the rapid induction of Fast expression in cells constitutively expressing high levels of Fas. Furthermore, the addition of soluble Fas-IgG fusion protein to the SEB-restimulated cultures blocked AICD and resulted in a 2 degrees proliferative response that was comparable in magnitude and kinetics to that of the lpr and gld T cells. The rapid onset of ***apoptosis*** in normal T cells subsequent to restimulation with SEE was in direct contrast to the proliferative response of the initial cultures, even though comparable levels of Fas and Fast RNA were found in T cells after 1 degrees and 2 degrees challenge. The clonal expansion of the normal T cells responding to the initial SEE stimulation was, however, dramatically compromised when the normal cells were cocultured with an MRL-lpr responder

population; addition of soluble Fas-IgG rescued the normal component of the response. Together, these data demonstrate first, that Fas/FasL interactions are intimately tied to superantigen-induced AICD, a form of autocrine cell death, and second, that Fast-mediated cytotoxicity is responsible for the disappearance of normal CD4(+) T cells in lpr cocultures.

L45 ANSWER 28 OF 31 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.DUPLICATE 9
ACCESSION NUMBER: 95006527 EMBASE
TITLE: In vivo depletion of Thy-1-positive cells originating from normal bone marrow abrogates the ***suppression*** of gld disease in normal-gld mixed bone marrow chimeras.
AUTHOR: MacDonald G.C.; Kakkanaiah V.N.; Sobel E.S.; Cohen P.L.; Eisenberg R.A.
CORPORATE SOURCE: CB 7280, 932 FLOB, University of North Carolina, Chapel Hill, NC 27599-7280, United States
SOURCE: Journal of Immunology, (1995) 154/1 (444-449). ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Mice homozygous for gld develop an ***autoimmune*** syndrome characterized by hypergammaglobulinemia, massive accumulation of abnormal T cells and the production of autoantibodies. Previous studies in our laboratory have shown that reconstitution of lethally irradiated B6/gld recipients with a mixture of normal and gld bone marrow (BM) ***suppresses*** the gld-induced syndrome. In this report we extend this observation by demonstrating that the depletion of normal Thy-1+ cells, but not normal B cells, restores gld disease in mixed BM chimeras congenic for Thy-1 and IgH alleles. These results strongly suggest that normal T cells ***suppress*** the development of gld-related abnormalities. It is probable that the mechanism by which normal Thy-1+ cells mediate the ***suppression*** is ***Fas*** ***ligand*** dependent.

L45 ANSWER 29 OF 31 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95211297 EMBASE
TITLE: Autoimmunity, ***apoptosis*** defects and retroviruses.
AUTHOR: Mountz J.D.; Cheng J.; Su X.; Wu J.; Zhou T.
CORPORATE SOURCE: Department of Medicine, Birmingham Veterans Admin. Med. Ctr., University of Alabama, Birmingham, AL 35294-0007, United States
SOURCE: Advances in Experimental Medicine and Biology, (1995) 374/- (183-201). ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB ***Autoimmune*** disease in both mice and humans is associated with increased expression of endogenous retroviruses in the thymus and T cells, and loss of self- ***tolerance*** by T cells. The basic genetic defect underlying ***autoimmune*** disease has been identified as a mutation of the Fas ***apoptosis*** antigen in MRL-lpr/lpr mice or a mutation of the ***Fas*** ***ligand*** in C3H-gld/gld mice. In MRL- lpr/lpr mice, the lpr mutation results from a 5.3 kb insertion of the ETn retrotransposon in the second intron of the Fas gene. In contrast to normal mice, which express a 2.2 kb normal size Fas cDNA, MRL-lpr/lpr mice express multiple Fas RNA transcripts ranging from 2-10.5 kb. In addition, a 5.7 kb full-length ETn transcript is highly expressed in the thymus of younger MRL- lpr/lpr mice. To determine if high ETn expression was dependent on abnormal Fas expression, CD2-fas transgenic mice were produced using the full-length murine Fas cDNA under the regulation of the CD2 promoter and enhancer. This resulted in normalization of Fas expression and also elimination of expression of the ETn retrotransposon. The ETn regulatory sequence contains potential DNA binding sites found in the enhancers of many genes activated during early T cell development in the thymus including enhancer regions for the TCR, CD3 and IL-2 genes. Therefore we propose that ETn expression is increased during early T cell development in the thymus, or after T cell activation, and that the integration of ETn in the Fas ***apoptosis*** gene leads to abnormal T cell ***apoptosis*** or development. Human ***autoimmune*** disease has also been found to result from production of a soluble inhibitor of ***apoptosis*** . The full-length cDNA and genomic clones for human Fas were cloned and sequenced. Patients with SLE produced high levels of an alternatively spliced soluble Fas (sFas) RNA lacking the transmembrane (exon 6) resulting in high circulating levels of the Fas molecule. This human sFas molecule was able to inhibit ***apoptosis*** in vitro at levels found in serum of SLE patients (200 ng/ml). The same levels of mouse sFas were able to inhibit ***apoptosis*** in vivo in mice resulting in a 3-fold increase in spleen size, and altered thymocyte maturation consisting of increased production of CD4-CD8- T cells and decreased CD4+CD8+ T cells. Regulation of Fas signaling in human T cells also plays a role in abnormal ***apoptosis*** . Fas signaling is mediated by the hematopoietic stem cell phosphatase, (Hcph) and is inhibited in the Hcph deficient Molt-4 T cell, the phosphatase deficient motheaten (me/me) mice and by the tyrosine phosphatase inhibitor pervanadate. Multiple pathways of Fas ***apoptosis*** were also shown to exist, as Fas induced ***apoptosis*** is increased in the liver of me/me mice, and signaling likely also involves an sphingomylinase-ceramide activated kinase pathway as utilized by the TNF-R. ***Fas*** ***ligand*** has been recently cloned in mice and humans, and is homologous to TNF-.alpha.. The ***Fas*** ***ligand*** defect in ***autoimmune*** C3H-gld/gld mice is due to a point mutation resulting in a single amino acid change in the hydrophobic region of the ***Fas*** ***ligand*** trimer. These results indicate that T cell ***apoptosis*** can be dramatically increased or decreased by cellular interactions which in turn regulate either the levels of production or signaling activity of the Fas and ***Fas*** ***ligand*** . Retroviruses and their products can influence ***apoptosis*** by altering expression of Fas or Fas-L, or altering apoptotic signaling after Fas/Fas-L interactions. Further insights into the regulation of ***apoptosis*** molecules will be important in normalizing this activity when it is decreased as in the case of ***autoimmune*** disease, or when it is in excess, as is the case with HIV disease.

L45 ANSWER 30 OF 31 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94341305 EMBASE
TITLE: ***Autoimmune*** disease: A problem of defective ***apoptosis*** .
AUTHOR: Mountz J.D.; Wu J.; Cheng J.; Zhou T.
CORPORATE SOURCE: Clinical Immunology/Rheumatol. Div., University of Alabama, UAB Station, 701 South 19th Street, Birmingham, AL 35294-0007, United States
SOURCE: ARTHRITIS RHEUM., (1994) 37/10 (1415-1420). ISSN: 0004-3591 CODEN: ARHEAW
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Human ***autoimmune*** diseases share the common feature of an imbalance between the production and destruction of various cell types including lymphocytes (SLE), synovial cells (RA), and fibroblasts (scleroderma). Patients with SLE have increased levels of soluble Fas that inhibit proper ***apoptosis*** of lymphocytes. In animal models of ***autoimmune*** diseases, mutations of genes involved in ***apoptosis*** including Fas, ***Fas*** ***ligand*** , and the hematopoietic cell phosphatase gene have been identified. Oncogenes, including bcl-2, p53, and myc, that regulate ***apoptosis*** are also expressed abnormally. Potent inducers of ***apoptosis*** including steroids, azathioprine, cyclophosphamide, and methotrexate are the most efficacious therapies for ***autoimmune*** disease currently known. Specific therapies that induce ***apoptosis*** without incurring side effects should improve treatment of ***autoimmune*** disease.

L45 ANSWER 31 OF 31 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 95102496 MEDLINE
DOCUMENT NUMBER: 95102496
TITLE: A family of ligands for the TNF receptor superfamily.
AUTHOR: Cosman D
CORPORATE SOURCE: Department of Molecular Biology, Immunex Research and Development Corporation, Seattle, Washington 98101.
SOURCE: STEM CELLS, (1994 Sep) 12 (5) 440-55. Ref: 121
Journal code: BN2. ISSN: 1066-5099.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
AB Recent progress in the definition of molecules involved in immune regulation has led to the discovery of a number of type I membrane glycoproteins with a distinctive, cysteine-rich, repetitive domain structure within their extracellular regions. Because the prototype members of this family are receptors for cytokines (tumor necrosis factor [TNF] and nerve growth factor [NGF]), it was expected that the ligands for the other receptors would possess cytokine-like activities. This prediction has been fulfilled by the cloning of cDNA encoding a series of type II membrane glycoproteins, with homology to TNF, that bind to, and signal through, their cognate receptors. While the biological role of some of these ligand-receptor pairs remains obscure, at least two members of the family, CD40 and Fas, have proven their importance. The human X-linked immunodeficiency, hyper IgM syndrome, is the result of mutations in the CD40 ligand gene, and the Fas and ***Fas*** ***ligand*** genes are mutated in two mouse strains, lpr and gld, that develop ***autoimmune*** disease. These findings, together with other evidence, point to key roles of CD40/CD40 ligand interactions in immune activation, particularly in T-dependent B cell responses, and of Fas/ ***Fas*** ***ligand*** in ***apoptosis*** and peripheral ***tolerance*** . These molecules, as well as the other ligands of the family, share the property of costimulation of T cell proliferation and are all expressed by activated T cells. More detailed analysis of the expression patterns of ligands and receptors on lymphocyte subpopulations will be necessary to define their different roles in immune activation and ***suppression*** .

=> d his

(FILE 'HOME' ENTERED AT 12:39:51 ON 06 JUL 1998)

FILE 'MEDLINE, BIOSIS, EMBASE, SCISEARCH, WPIDS, USPATFULL' ENTERED
AT 12:40:20 ON 06 JUL 1998
L1 3121 S FAS(W)LIGAND
L2 0 S ANTIGEN PRESENTING CALLAS
L3 20244 S ANTIGEN PRESENTING CELLS
L4 899454 S ANTIGEN
L5 1159917 S TOLERANCE OR SUPPRESS?
L6 81258 S APOPTOSIS
L7 586080 S T CELL OR T CELLS OR T LYMPHOCYTE OR T LYMPHOCYTES
L8 52054 S ADENOVIRUS
L9 2957 S ADENO-ASSOCIATED VIRUS
L10 1300524 S VIRUS OR VIRAL
L11 17950 S ALLOANTIGEN OR TRANSPLANTATION ANTIGEN OR FOREIGN ANTIG
L12 10392 S AUTOANTIGEN OR AUTOLOGOUS ANTIGEN OR HOMOGENEIC
L13 137585 S AUTOIMMUNE
L14 511 S CRMA
L15 35119 S CYTOTOXIC T CELL OR CYTOTOXIC T CELL OR CTL
L16 13699 S CD4 HELPER CELLS OR CD4 CELLS
L17 33979 S GENE THERAPY
L18 3062365 S INHIBIT?
L19 19608 S TRANSGENE

L20 1810 S VIRAL VECTOR
L21 17 S L5 AND L4 AND L3 AND L1
L22 12 DUP REM L21 (5 DUPLICATES REMOVED)
L23 408 S L14 AND L6
L24 0 S L14 AND L6 AND L3
L25 10 S L14 AND L6 AND L15
L26 4 DUP REM L25 (6 DUPLICATES REMOVED)
L27 0 S L17 AND L1 AND L3 AND L5
L28 10 S L17 AND L1 AND L5
L29 7 DUP REM L28 (3 DUPLICATES REMOVED)
L30 0 S L19 AND L3 AND L20 AND L6 AND L1
L31 0 S L19 AND L20 AND L6 AND L1
L32 2 S L20 AND L6 AND L1
L33 7 S L1 AND L6 AND L11
L34 5 DUP REM L33 (2 DUPLICATES REMOVED)
L35 39 S L1 AND L6 AND L8
L36 19 DUP REM L35 (20 DUPLICATES REMOVED)
L37 1 S L1 AND L6 AND L9
L38 292 S L1 AND L6 AND L10
L39 41 S L38 AND L5
L40 27 DUP REM L39 (14 DUPLICATES REMOVED)
L41 3 S L1 AND L6 AND L12
L42 3 DUP REM L41 (0 DUPLICATES REMOVED)
L43 286 S L1 AND L6 AND L13
L44 52 S L1 AND L6 AND L13 AND L5
L45 31 DUP REM L44 (21 DUPLICATES REMOVED)

=> logoff

ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y

STN INTERNATIONAL LOGOFF AT 13:12:06 ON 06 JUL 1998